

資料 3 - 1 - 4

既存化学物質の人健康影響に関する情報（第一種特定化学物質審議関係①）

（平成 17 年 11 月 18 日）

No. 17 2- (2H-1, 2, 3-ベンゾトリアゾール-2-イル) -4, 6-ジ- t e r t -ブチルフェノール…p. 1

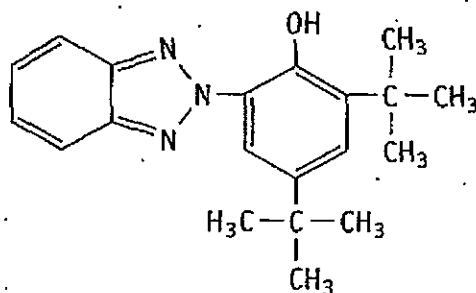
2-(2'-Hydroxy-3',5'-di-tert-butylphenyl)benzotriazole

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾール

[CAS No. 3846-71-7]

Molecular formula: $C_{20}H_{25}N_3O$

Molecular weight: 323.44



ABSTRACT

A single dose oral toxicity test of 2-(2'-hydroxy-3',5'-di-tert-butylphenyl)benzotriazole was conducted at doses of 0 and 2000 mg/kg using male and female rats. No deaths were observed in the 0 or 2000 mg/kg groups in either sex, pointing to an LD_{50} value higher than 2000 mg/kg in both sexes.

A repeated dose toxicity test was conducted at doses of 0, 0.5, 2.5, 12.5 and 62.5 mg/kg/day using male and female rats. No deaths of either sex were observed in any of the treatment groups.

The hematocrit value, hemoglobin concentration, and red blood cell count were lowered in males of the 2.5 mg/kg or higher dose groups. The MCHC was lowered in males of the 12.5 and 62.5 mg/kg groups and the fibrinogen concentration was reduced in males of the 2.5 mg/kg or higher dose groups and in females of the 62.5 mg/kg group.

The serum level of glucose was higher in males of the 2.5 mg/kg or higher dose groups and in females of the 62.5 mg/kg group. The total cholesterol and triglyceride levels were elevated in females of the 62.5 mg/kg group.

The liver weights were increased in males of the 0.5 mg/kg or higher dose groups and in females receiving 12.5 mg/kg or higher. The kidney weights were elevated in males of the 62.5 mg/kg group.

Macroscopically, enlarged livers with white patch zones were observed. Histopathologically, the following were noted: degeneration of the myocardium, with cellular infiltration and hypertrophy, extramedullary hematopoiesis of the spleen, vacuolar degeneration, hypertrophy of hepatocytes, increase in mitosis, proliferation of bile ducts and focal necrosis in the liver, basophilic tubules and dilatation of tubules, hypertrophy of tubular epithelium of collecting tubules in the kidney, and follicular cell hyperplasia in the thyroid gland.

These changes were observed in all the treated groups except females dosed 0.5 mg/kg.

The NOEL for repeated dose toxicity is considered to be less than 0.5 mg/kg/day for males and 2.5 mg/kg/day for females.

Genotoxicity of 2-(2'-hydroxy-3',5'-di-*tert*-butylphenyl)benzotriazole was studied by a reverse mutation test in bacteria. This substance was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 or *Escherichia coli* WP2' *uvrA*, with or without an exogenous metabolic activation system.

Genotoxicity of 2-(2'-hydroxy-3',5'-di-*tert*-butylphenyl)benzotriazole was studied by chromosomal aberration test in cultured Chinese hamster lung (CHL/IU) cells.

2-(2'-Hydroxy-3',5'-di-*tert*-butylphenyl)benzotriazole did not induce structural chromosomal aberrations or polyploidy up to 3.2 mg/mL (10 mmol/L) under the present test conditions.

SUMMARIZED DATA FROM THE STUDIES

1. Single Dose Oral Toxicity ¹⁾

| | |
|---------------------|---------------------------|
| Purity | : 100 % |
| Test species/strain | : Rat/Crj:CD(SD)IGS |
| Test method | : OECD Test Guideline 401 |
| Route | : Oral (gavage) |
| Dosage | : 0 (vehicle), 2000 mg/kg |
| Number of animals | : Males and females; 5 |
| Vehicle | : Corn oil |
| GLP | : Yes |

Test results:

No deaths were observed in the 0 or 2000 mg/kg group in either sex. The LD₅₀ value is higher than 2000 mg/kg in both sexes.

2. Repeated Dose Oral Toxicity ¹⁾

| | |
|-----------------------|--|
| Purity | : 100 % |
| Test species/strain | : Rat/Crj:CD(SD)IGS |
| Test method | : Guideline for the 28-Day Repeated Dose Toxicity Test in Mammalian Species (Chemical Substances Control Law of Japan) |
| Route | : Oral (gavage) |
| Dosage | : 0 (vehicle), 0.5, 2.5, 12.5, 62.5 mg/kg/day |
| Number of animals | : Males and females; 5 |
| Vehicle | : Corn oil |
| Administration period | : Males and females, 28 days |
| Terminal killing | : Males and females, days 29 or 43 |
| GLP | : Yes |

Test results:

No deaths were observed in any of the treatment groups in either sex. There were also no changes in general appearance or body weights.

Hematological examination demonstrated, the hematocrit value, hemoglobin concentration, and red blood cell count to be lowered in males in the 2.5 mg/kg or higher dose groups. The MCHC was lowered in males in the 12.5 and 62.5 mg/kg groups.

2-(2'-Hydroxy-3',5'-di-*tert*-butylphenyl) benzotriazole [3846-71-7]

On blood coagulation examination, the fibrinogen concentration was found to be lowered in males of the 2.5 mg/kg or higher dose groups and in females of the 62.5 mg/kg group. With the blood chemical examination, the serum level of glucose was elevated in males of the 2.5 mg/kg or higher dose groups and in females of the 62.5 mg/kg group. The total cholesterol and triglyceride levels were higher in females of the 62.5 mg/kg group than in the controls.

The absolute and relative liver weights were increased in males of the 0.5 mg/kg or higher dose groups and in females of the 12.5 mg/kg or higher dose groups. Absolute and relative kidney weights were elevated in males of the 62.5 mg/kg group.

Macroscopically, enlarged livers with white patches were observed.

Histopathologically, the following changes were observed: degeneration of myocardium, with cellular infiltration and hypertrophy, extramedullary hematopoiesis of the spleen, vacuolar degeneration and hypertrophy of hepatocytes, with increased mitosis, bile duct proliferation and focal necrosis in the liver, basophilic tubules and dilatation of tubules, with hypertrophy of tubular epithelium of collecting tubules in the kidneys, and follicular cell hyperplasia in the thyroid gland.

These changes were observed in all the treated groups except females dosed 0.5 mg/kg.

The NOEL for repeated dose toxicity is considered to be less than 0.5 mg/kg/day for males and 2.5 mg/kg/day for females.

3. Genetic Toxicity

3-1. Bacterial test ²⁾

| | |
|----------------------|---|
| Purity | : 100 % |
| Test species/strains | : <i>Salmonella typhimurium</i> TA100, TA1535, TA98, TA1537, <i>Escherichia coli</i> WP2 <i>uvrA</i> |
| Test method | : Guidelines for Screening Mutagenicity Testing of Chemicals (Chemical Substances Control Law of Japan) and OECD Test Guideline 471 |
| Procedures | : Pre-incubation method |
| Solvent | : Dimethyl sulfoxide |
| Positive controls | : -S9 mix; 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (TA100, TA98, WP2 <i>uvrA</i>), Sodium azide (TA1535) and 9-Aminoacridine (TA1537) +S9 mix; 2-Aminoanthracene (five strains) |
| Dosage | : -S9 mix; 0, 313, 625, 1250, 2500, 5000 μ g/plate (five strains) +S9 mix; 0, 313, 625, 1250, 2500, 5000 μ g/plate (five strains) |
| S9 | : Rat liver, induced with phenobarbital and 5,6-benzoflavone |
| Plates/test | : 3 (1 for cytotoxicity test) |
| Number of replicates | : 2 (plus 1 cytotoxicity test) |
| GLP | : Yes |

Test results:

This chemical did not induce gene mutations in *S. typhimurium* TA100, TA98, TA1535, TA1537 or *E. coli* WP2 *uvrA* strains with or without S9 mix. Growth inhibition was not observed up to 5000 μ g/plate in any strain, with or without S9 mix.

Genetic effects:

Salmonella typhimurium TA100, TA98, TA1535, TA1537

| | + | ? | - |
|-------------------------------|-----|-----|-----|
| Without metabolic activation: | [] | [] | [*] |
| With metabolic activation: | [] | [] | [*] |

Escherichia coli WP2 *uvrA*

| | + | ? | - |
|-------------------------------|-----|-----|-----|
| Without metabolic activation: | [] | [] | [*] |
| With metabolic activation: | [] | [] | [*] |

3-2. Non-bacterial *in vitro* test (chromosomal aberration test)²⁾

| | |
|-------------------|--|
| Purity | : 100 % |
| Type of cell used | : Chinese hamster lung (CHL/IU) cells |
| Test method | : Guidelines for Screening Mutagenicity Testing of Chemicals (Chemical Substances Control Law of Japan) and OECD Test Guideline 473 |
| Vehicle | : 0.5 % Sodium carboxymethylcellulose |
| Positive controls | : -S9 mix; Mitomycin C +S9 mix; Cyclophosphamide |
| Dosage | : -S9 mix (continuous treatment) : 0, 0.80, 1.6, 3.2 mg/mL -S9 mix (short-term treatment) : 0, 0.80, 1.6, 3.2 mg/mL +S9 mix (short-term treatment) : 0, 0.80, 1.6, 3.2 mg/mL |
| S9 | : Rat liver, induced with phenobarbital and 5,6-benzoflavone |
| Plates/test | : 2 |
| GLP | : Yes |

Test results:

With all the test systems, cells with structural chromosomal aberrations and polyploidy were not significantly increased at any dose.

Genotoxic effects:

| | clastogenicity | | | polyploidy | | |
|-------------------------------|----------------|-----|-----|------------|-----|-----|
| | + | ? | - | + | ? | - |
| Without metabolic activation: | [] | [] | [*] | [] | [] | [*] |
| With metabolic activation: | [] | [] | [*] | [] | [] | [*] |

- 1) The tests were performed by the Biosafety Research Center, Foods, Drugs and Pesticides (An-Pyo Center), 582-2 Shiosinden Arahama, Fukude-Cho, Iwata-Gun, Shizuoka, 437-1213, Japan. Tel +81-538-58-1266 Fax +81-538-58-1393
- 2) The tests were performed by the Hatano Research Institute, Food and Drug Safety Center, 729-5-Ochiai, Hadano-shi, Kanagawa, 257-8523, Japan. Tel +81-463-82-4751 Fax +81-463-82-9627

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールの ラットを用いる単回経口投与毒性試験

Single Dose Oral Toxicity Test of 2-(2'-Hydroxy-3',5'-di-tert-butylphenyl) benzotriazole in Rats

要約

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールは主にプラスチックの紫外線吸収剤として用いられている。2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールの単回経口投与毒性試験をCD(SD)IGS系(SPF)雌雄ラットを用いて実施した。

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールはコーンオイルに懸濁し、雌雄ともに2000 mg/kgを単回強制経口投与した。また、媒体対照としてコーンオイルのみを投与した群も設定した。観察期間は14日間とし、一般状態の観察、体重推移および病理学検査を実施した。

観察期間を通じて雌雄ともに一般状態に異常所見は観察されず、死亡例も認められなかった。体重測定では、雌雄とも対照群に比較して投与後7および14日の測定値に差が認められなかった。

病理学検査では、雌雄ともに異常所見は認められなかった。

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールのラットにおけるLD₅₀値は雌雄ともに2000 mg/kgより大であった。

方法

1. 物質

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾール[シプロ化成(株)(福井)、純度100%、Lot No. S4-034-1]は白色粉末であり、使用時まで室温の被験物質保管庫に保管した。試験終了後、残余被験物質を提収元で再分析し、被験物質が試験期間中安定であったことを確認した。

投与液は、被験物質をコーンオイル(ナカライテスク社、Lot No. V7B5849)に懸濁し200 mg/mLの濃度となるように調製した。投与液は投与直前に調製した。投与中の被験物質濃度を調製後速やかに測定した結果、適時に調製されていたことが確認された。

2. 投与量の設定および投与方法

本試験に先立って実施した予備試験において2000 mg/kgを投与した結果、雌雄とも一般状態に変化が観察されず死亡例もみられなかった。従って、本試験の用いる雌雄ともにOECDガイドライン「急性経口」で上限用量として指定されている2000 mg/kgを設定し、さら

に媒体対照群を設定した。投与容量は体重100 g当たり1.0 mLとし、個体別に測定した体重に基づいて投与液量を算出した。

投与回数は1回とし、投与前約16時間絶食させた動物に胃ゾンダを用いて強制経口投与した。なお、対照群にはコーンオイルのみを投与した。給餌は、被験物質投与後約3時間に行った。

3. 供試動物

5週齢のCrj:CD(SD)IGS系ラット(SPF)雌雄各16匹を日本チャールス・リバー(株)から購入し、試験環境への馴化のため1週間予備飼育を行い、6週齢に達した時点で投与した。

動物は23.4~24.3 °C、湿度51~67%、照明時間12時間(午前7時点灯、午後7時消灯)に制御された飼育室で、ステンレス製網目飼育ケージに5匹ずつ収容して飼育した。動物には、オリエンタル酵母工業(株)製造の固型飼料MF(Lot No. 010205)および水道水を自由に摂取させた。

4. 群構成

動物はあらかじめ体重によって層別化し、無作為抽出法により雌雄ともに各群5匹ずつ振り分けた。投与時の体重は、雄が157~176 g、雌が126~141 gであった。

5. 観察および検査

中毒症状および生死の観察は、投与6時間までは1時間毎に、投与翌日からは1日1~2回、14日間にわたって実施した。体重は投与直前、投与後7および14日に測定した。観察終了時に全ての動物をエーテル麻酔後放血死させ解剖した。

結果

1. 死亡率およびLD₅₀値

雌雄の対照群および2000 mg/kg群に死亡例は認められなかった。従って、LD₅₀値は雌雄ともに2000 mg/kgより大であった。

2. 一般状態

観察期間を通じていずれの動物にも一般状態に異常は認められなかった。

3. 体重

対照群に比較して雌雄の2000 mg/kg群で投与後7お

単回経口投与毒性試験

よび14日の測定時とも差がみられなかった。

4. 病理所見

観察期間終了時の解剖でいずれの動物にも異常所見は認められなかった。

考察

2-(2'-ヒドロキシ-3',5'-ジ-*tert*-ブチルフェニル)ベンゾトリアゾールの2000 mg/kgを6週齢のCrj:CD(SD)IGS系ラットの雌雄に単回経口投与し、投与後14日間観察した。雌雄とも一般状態に異常は観察されず、死亡例も認められなかった。観察期間中、体重は雌雄とも順調な推移を示した。また、生存動物の病理解剖においても異常所見は認められなかった。

従って2-(2'-ヒドロキシ-3',5'-ジ-*tert*-ブチルフェニル)ベンゾトリアゾールのLD₅₀値は雌雄ともに2000 mg/kgより大と考えられた。

連絡先

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2-(2'-ヒドロキシ-3',5'-ジ-*tert*-ブチルフェニル)ベンゾトリアゾールの
ラットを用いる28日間反復経口投与毒性試験

Twenty-eight-day Repeat Dose Oral Toxicity Test
of 2-(2'-Hydroxy-3',5'-di-*tert*-butylphenyl)benzotriazole in Rats

要約

2-(2'-ヒドロキシ-3',5'-ジ-*tert*-ブチルフェニル)ベンゾトリアゾールの28日間反復経口投与毒性試験を雌雄のCD(SD)IGS系ラット(SPF)を用いて実施した。

1群雌雄各5匹のラットからなる5試験群を設定し、さらに対照群および最高用量群には雌雄各5匹のラットを追加して回復群を設定した。

被験物質をコーンオイルに懸濁して、0, 0.5, 2.5, 12.5および62.5 mg/kgに相当する量を毎日1回、4週間反復経口投与し、一般状態の観察、体重測定、摂餌量測定、血液学検査、血液凝固能検査、血液生化学検査、尿検査、器官重量測定および病理学検査を行った。なお、回復期間は2週間とし、投与終了時と同様の検査を実施した。

投与期間および回復期間を通して対照群および各投与群で一般状態に異常は観察されず、死亡例も認められなかった。

体重は、各投与群の雌雄において差は認められなかった。

摂餌量は、62.5 mg/kg群の雌雄で高値を示した週がみられ、総摂餌量も高値あるいは高値傾向であった。飼料効率は62.5 mg/kg群の雄で低値を示し、投与期間の平均飼料効率も低値であった。

血液学検査では、2.5 mg/kg以上の群の雄でヘマトクリット値、ヘモグロビン量および赤血球数が低値を示した。さらに、12.5および62.5 mg/kg群の雄でMCHCが低値を示した。回復期間終了時にも62.5 mg/kg群の雄でヘマトクリット値、ヘモグロビン量、赤血球数、MCHおよびMCHCが低値、網赤血球比率の高値が認められた。血液凝固能検査では、2.5 mg/kg以上の群の雄および62.5 mg/kg群の雌でフィブリノーゲン量が低値を示した。回復期間終了時では、フィブリノーゲン量が62.5 mg/kg群の雌で高値を示したが雄では差がなかった。

血液生化学検査では、2.5 mg/kg以上の群の雄および62.5 mg/kg群の雌で血糖値が高値を示した。62.5 mg/kg群の雌で総コレステロールおよび中性脂肪の濃度が高値を示した。12.5 mg/kg以上の群の雄でアルブミン濃度が高値、0.5 mg/kg以上の群の雄および62.5 mg/kg群の雌でA/G比が高値を示した。12.5 mg/kg以上の群の雄および62.5 mg/kg群の雌でALT活性が高値、62.5 mg/kg群の雄でAST活性が高値を示した。12.5および62.5 mg/kg群の雄でALP活性が高値を示した。62.5 mg/kg

群の雄で尿素窒素濃度が高値を示した。回復期間終了時には62.5 mg/kg群の雌雄でアルブミン濃度の高値および総ビリルビン濃度が低値を示した。雄では尿素窒素濃度、A/G比、ALTおよびALPの活性が、雌では血糖値、総コレステロールおよび総蛋白の濃度がいずれも高値を示し、休薬しても回復を示さないと考えられた。

器官重量では、0.5 mg/kg以上の群の雄および12.5 mg/kg以上の群の雌で肝臓絶対重量が高値あるいは高値傾向を示した。62.5 mg/kg群の雄では腎臓絶対重量が高値を示した。回復期間終了時では62.5 mg/kg群の雌雄で肝臓絶対重量が高値を示した。器官重量/体重比(相対重量)では0.5 mg/kg以上の群の雄および12.5 mg/kg以上の群の雌で肝臓相対重量が高値を示した。また、62.5 mg/kg群の雄で腎臓相対重量が高値を示した。回復期間終了時では62.5 mg/kg群の雌雄で肝臓相対重量が、雄で腎臓相対重量が高値を示しており、休薬しても回復を示さないと考えられた。

解剖所見では、被験物質の影響を示唆する病変として、投与期間終了時において、肝臓の肥大が0.5 mg/kg以上の群の雄および12.5 mg/kg以上の群の雌、白色斑/区域が2.5 mg/kg以上の群の雄および62.5 mg/kg群の雌に観察され、回復期間終了時においても同様の所見が62.5 mg/kg群において観察された。病理組織所見では、投与期間終了時において心臓の心筋変性、細胞浸潤および心筋肥大が雌雄に、脾臓の髓外造血が雄に、肝臓において小葉辺縁部の肝細胞の空胞変性、肝細胞肥大、分裂像増多および胆管増殖が雌雄に、巣状壊死が雄に、腎臓の尿細管好塩基化の程度の増強が雄に、管腔拡張が雄に、集合管の尿細管上皮肥大が雌雄に、甲状腺の濾胞細胞増生が雌雄に観察された。回復期間終了時の62.5 mg/kg群において、投与終了時に観察された同様の諸所見が心臓、脾臓、肝臓および甲状腺に観察された。

以上のように、本試験条件下における2-(2'-ヒドロキシ-3',5'-ジ-*tert*-ブチルフェニル)ベンゾトリアゾールの無影響量は、雌では12.5 mg/kg群で肝臓の絶対重量および相対重量の高値、肝臓の肥大、肝細胞肥大が認められたことから2.5 mg/kg/day、また、雄では0.5 mg/kg群で肝臓絶対重量の高値傾向および相対重量の高値、肝臓の肥大、肝細胞肥大が認められたことから0.5 mg/kg/day未満と判断された。

方法

1. 被験物質および投与液の調製

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾール[シプロ化成(株)(福井), Lot No. S4-034-1, 純度100%]は常温で安定な白色粉末の化合物である。投与終了後、残余被験物質を提供元で再分析し、被験物質が試験期間中安定であったことを確認した。

投与液は被験物質をコーンオイル(Lot No. V1A1849, ナカライテスク(株))に懸濁して0.1, 0.5, 2.5および12.5 mg/mLの濃度となるように調製した。なお、コーンオイル中の2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールは冷蔵保存条件下で7日間安定であることから、投与液の調製は毎週1回実施し、1日分ずつ小分けして投与まで冷蔵庫に保管した。全ての試験群の投与液について適切に調製されていることを確認するため、初回および最終調製時に各投与液の一部を分取し、被験物質濃度を測定した。その結果、初回調製時は設定濃度の94.2~104.3%および最終調製時は99.6~103.4%であり、適切に調製されていることが確認された。

2. 動物および飼育方法

4週齢のCrj:CD(SD)IGS系ラット(SPF)雌雄各52匹を日本チャールス・リバー(株)から購入し、検収後9日間、試験環境に馴化させた後、体重増加が順調で一般状態に異常を認めなかった雌雄各35匹(計70匹)を選び、5週齢で投与を開始した。動物は群分け当日の体重に基づいて層別化し、平均体重が均等となるように各群に割り付けた。投与開始時の体重は雄で136~153g, 雌で111~127gであった。試験群は0, 0.5, 2.5, 12.5および62.5 mg/kgの5群とし、1群雌雄各5匹を用い、0および62.5 mg/kg群に雌雄各5匹を追加して回復群を設定した。

動物は、温度21.4~25.9℃, 湿度51~75%, 換気回数1時間20回, 照明12時間(午前7時点灯, 午後7時消灯)に設定されたバリアシステム飼育室で飼育した。アルミ製前面・床ステンレス網目飼育ケージに動物を1匹ずつ収容し、オリエンタル酵母工業(株)製造の放射線滅菌したラット、マウス飼料CRF-1(Lot No. 010406)および水道水を自由に摂取させた。飼育ケージは隔週1回、給餌器は週1回取り換えた。

3. 投与量の設定および投与方法

投与量設定のため雌雄とも0, 100, 300および1000 mg/kgの4用量で2週間反復投与試験を実施した結果、100, 300および1000 mg/kg群の雌雄において肝臓の絶対重量および相対重量が高値を示した。特に相対重量の増加率は雄で131~165%, 雌で80~138%であった。肝臓相対重量の増加率を指標として解析した結果、肝臓に影響のみられない用量を1~3 mg/kgと推定した。以上の成績を基に28日間反復投与毒性試験の投与期間を考慮して肝臓に影響認められないと推定される用量0.5 mg/kgを低用量とした。さらに公比5で乗し中用量を2.5 mg/kg, 高用量を12.5 mg/kgおよび最高用量を

62.5 mg/kgと設定した。

投与液量は体重100g当たり0.5 mLとし、個体別に測定した体重に基づいて投与液量を算出し、1日1回胃ゾンデを用いて強制経口投与した。対照群にはコーンオイルのみを同様に投与した。なお、回復期間は14日間とした。

4. 観察および検査

1) 一般状態の観察

全動物を投与期間中は投与前、投与後1および5時間、回復期間は午前および午後を観察し、中毒症状の有無や行動異常を記録した。

2) 体重

投与開始時から回復期間終了時まで毎週1回測定した。

3) 摂餌量

給餌した飼料の残量を毎週1回、測定し、摂餌量(g/day)および飼料効率(%)を算出した。

4) 血液学検査

投与期間終了時および回復期間終了時の計2回実施した。採血するに当たり、動物は約16時間絶食させた。動物をエーテルで麻酔して開腹し、腹部大動脈から採血した。

採取した血液の一部にEDTA-2Kを添加し、白血球数(WBC:フローサイトメトリー), 赤血球数(RBC:暗視野板法), ヘモグロビン量(HGB:シアンメトヘモグロビン法), ヘマトクリット値(HCT:RBC, MCVより算出), 平均赤血球容積(MCV:暗視野板法), 平均赤血球色素量(MCH:HGB, RBCより算出), 平均赤血球色素濃度(MCHC:HGB, HCTより算出), 血小板数(PLT:暗視野板法), 白血球百分率(フローサイトメトリー)および網赤血球率(Reticulocyte:RNA染色法)を総合血液学検査装置ADVIA120(バイエル社)を用いて測定した。さらに、3.13%クエン酸ナトリウム水溶液添加血液の血漿を用いて、プロトロンビン時間(PT:Quick1段法), 活性化部分トロンボプラスチン時間(APTT:クロット法)およびフィブリノーゲン量(Fibrinogen:トロンビン時間法)を血液凝固自動測定装置KC-40(独国Amelung社)により測定した。

5) 血液生化学検査

血液学検査に引き続き採取した血液を静置後、遠心分離して得られた血清を用いて、総蛋白(T.protein:Biuret法), アルブミン(Albumin:BCG法), A/G比(A/G:総蛋白およびアルブミンより算出), 血糖(Glucose:HK-G-6-PDH法), 中性脂肪(Triglyceride:GK-GPO遊離グリセロール消去法), 総コレステロール(T.cholesterol:コレステロールオキシダーゼHDAOS法), 尿素窒素(BUN:ウレアーゼGLDH法), クレアチニン(Creatinine:酵素法), 総ビリルビン(T.bilirubin:バナジン酸酸化法), ア

スパラギン酸アミノトランスフェラーゼ(AST:酵素-UV法), アラニンアミノトランスフェラーゼ(ALT:酵素-UV法), アルカリホスファターゼ(ALP:P-ニトロフェニルリン酸基質法), γ -グルタミルトランスベプチターゼ(γ -GTP:L- γ -グルタミル3-カルボキシ4NA法), カルシウム(Calcium:MXB法)および無機リン(L.phosphorus:PNP-XDH法)を多項目生化学自動分析装置日立7170(日立製作所)により測定した。電解質のナトリウム(Sodium:イオン選択電極法), カリウム(Potassium:イオン選択電極法)および塩素(Chloride:イオン選択電極法)を電解質測定装置EA06R(堀エイアンドティー)を用いて測定した。

6) 尿検査

投与期間終了週および回復期間終了週に検査を実施した。すなわち、検査動物を代謝ケージに個別に収容し、飼料および飲料水を自由に与えて3時間尿(午前10時から午後1時まで)および24時間尿(午前10時から翌日午前10時まで)を採取した。3時間尿を用いて、N-マルティステックスSG(バイエルメディカル(株))と尿分析装置CLINITEK 500(バイエル社)でpH, 潜血, ケトン体, 糖, 蛋白, ビリルビン, ウロビリノーゲンを検査した。24時間尿を用いて、尿量, 色調, 尿浸透圧および尿沈渣を検査した。なお、尿浸透圧は、自動浸透圧測定装置OM-6030(堀アークレイファクトリー)を用いて氷点降下法で測定した。また、尿を1500 r.p.m.で5分間遠心し、残渣を用いてステルンハイマー変法による染色を施し、尿沈渣について鏡検した。

7) 病理学検査

投与期間終了時および回復期間終了時に動物をエーテル麻酔し、放血後解剖を実施した。解剖では動物の体表、体腔および諸器官について観察し、すべての肉眼異常(部)の大きさ、硬さなどを記録した。

器官重量は脳、心臓、肝臓、腎臓、副腎、胸腺、脾臓、精巣、精巣上体、卵巣、甲状腺(上皮小体を含む)および下垂体について測定した。器官重量/体重比(相対重量)は投与27日または回復13日の測定体重および器官重量から算出した。また、リンパ節(腸間膜, 下顎), 骨髄(大腿骨), 胸腺, 気管, 肺(気管支を含む), 心臓, 甲状腺, 上皮小体, 胃, 十二指腸, 空腸, 回腸(バイエル氏板を含む), 盲腸, 結腸, 直腸, 肝臓, 脾臓, 膵臓, 腎臓, 副腎, 膀胱, 精囊, 前立腺, 精巣, 精巣上体, 卵巣, 子宮, 陰, 眼球, 脳, 下垂体, 脊髄(頸部, 胸部, 腰部), 骨格筋(大腿部)および坐骨神経を10%中性緩衝ホルマリン液で固定した。なお、精巣および精巣上体はホルマリン酢酸液(FA液)で前固定した後、10%中性緩衝ホルマリン液で固定した。病理組織学検査は対照群および最高用量群の上記器官および組織について実施した。また、最高用量群の心臓, 脾臓, 肝臓, 腎臓および甲状腺で被験物質の影響と考えられる変化が認められたため、他の用量群および回復群についても実施した。組織標本は、常法に従ってパラフィン包埋、薄切後、ヘマトキシリ

ン・エオジン染色を施した。鏡検では、病変の種類および程度を含む各所見について記録した。

5. 統計解析

各試験群の体重, 摂餌量, 血液学検査値, 血液凝固能検査値, 血液生化学検査値, 尿検査値(尿量および浸透圧), 器官重量および器官重量/体重比は、最初にBartlettの等分散検定を実施した。等分散の場合はDunnettの多重比較検定^{1,2)}で対照群と各投与群間の有意差を検定した。Bartlettの等分散検定で不等分散の場合はSteelの検定³⁾で対照群と各投与群間の有意差を検定した。上記定量値の有意水準は5%および1%の両側検定で実施した。また、病理学検査結果の検定はFisherの確率計算法を用いた。

結果

1. 一般状態

投与期間では、0.5 mg/kg群の雌の1例に外傷/頸部が観察されたが、被験物質に関連する変化ではなかった。その他、対照群を含む各投与群の雌雄において変化は認められなかった。

回復期間では、対照群および62.5 mg/kg群の雌雄において変化は認められなかった。

2. 体重(Fig. 1)

投与期間では、対照群と各投与群の雌雄において差は認められなかった。

回復期間では、対照群および62.5 mg/kg群の雌雄において差は認められなかった。

3. 摂餌量

対照群と比較して62.5 mg/kg群の雄で投与14および21日に、雌で投与21および27日にいずれも高値を示し、総摂餌量も高値あるいは高値傾向を示した。

回復期間では、対照群と比較して62.5 mg/kg群の雌雄で差が認められなかった。

飼料効率では、対照群と比較して62.5 mg/kg群の雄で投与21および27日に低値を示し、平均飼料効率も低値を示した。

4. 血液学検査(Table 1)

[投与期間終了時]

対照群と比較して2.5 mg/kg以上の群の雄でヘマトクリット値, ヘモグロビン量および赤血球数が低値を示し、さらに12.5 mg/kg以上の群の雄でMCHCが低値を示した。また、62.5 mg/kg群の雄では血小板数が高値を示した。その他、2.5 mg/kg群の雄で単球比率が高値、12.5 mg/kg群の雄で網赤血球比率が高値を示したが、いずれも用量に依存した変化ではなかった。血液凝固能検査では、対照群と比較して2.5 mg/kg以上の群の雄および62.5 mg/kg群の雌でフィブリノーゲン量が低値を示した。その他、12.5および62.5 mg/kg群の雌ではPT

28日間反復投与毒性試験

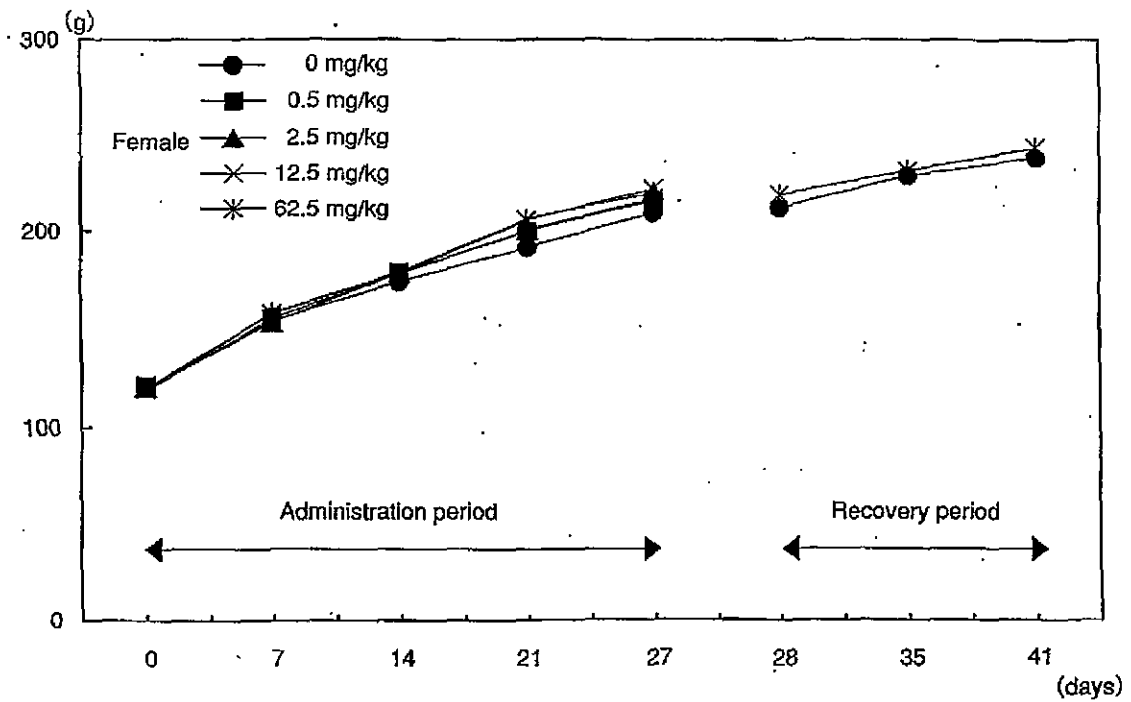
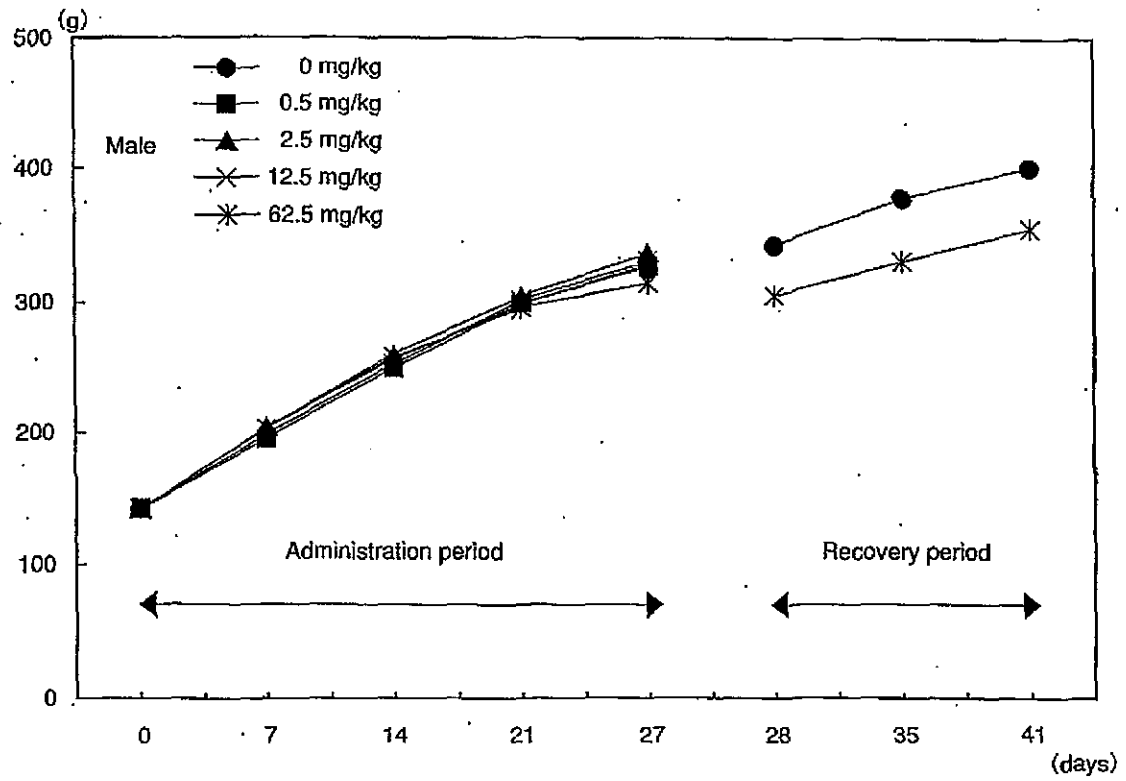


Fig. 1 Body weight of rats treated orally with 2-(2'-hydroxy-3',5'-di-*tert*-butylphenyl) benzotriazole in the twenty-eight-day repeat dose toxicity test

が短縮を示したが、軽微であり毒性学的に意義のある変化ではなかった。

[回復期間終了時]

対照群に比較して62.5 mg/kg群の雌雄で血小板数が高値を示した。また、62.5 mg/kg群の雄でヘマトクリット値、ヘモグロビン量、赤血球数、MCHおよびMCHCが低値、網赤血球比率が高値を示し、雌でフィブリノーゲン量が高値を示した。

その他、62.5 mg/kg群の雄で好酸球比率が低値を示したが軽微な変化であった。

5. 血液生化学検査 (Table 2)

[投与期間終了時]

対照群に比較して62.5 mg/kg群の雌雄、2.5および12.5 mg/kg群の雄で血糖値が高値を示した。62.5 mg/kg群の雄で総コレステロールおよび中性脂肪の濃度が高値を示した。12.5および62.5 mg/kg群の雄でアルブミン濃度が高値、各投与群の雄および62.5 mg/kg群の雄でA/G比が高値を示した。62.5 mg/kg群の雌雄および12.5 mg/kg群の雄でALT活性が高値、62.5 mg/kg群の雄でAST活性が高値を示した。12.5および62.5 mg/kg群の雄でALP活性が高値を示した。62.5 mg/kg群の雄で尿素窒素濃度が高値を示した。その他、0.5および2.5 mg/kg群の雄で総ビリルビン濃度が低値、2.5 mg/kg群の雄でナトリウム濃度が低値を示したがいずれも用量に依存した変化ではなかった。

[回復期間終了時]

対照群に比較して62.5 mg/kg群の雌雄でアルブミン濃度の高値および総ビリルビン濃度が低値を示した。雄では尿素窒素濃度、A/G比、ALTおよびALPの活性が、雌では血糖値、総コレステロールおよび総蛋白の濃度がいずれも高値を示した。

6. 尿検査 (Table 3)

[投与期間終了時]

対照群に比較して2.5 mg/kg群の雌で尿量が増加、尿浸透圧が低値を示したが用量に依存した変化ではなかった。

[回復期間終了時]

対照群に比較して62.5 mg/kg群の雌雄において検査したいずれの項目においても変化が認められなかった。

7. 器官重量 (Table 4)

[投与期間終了時]

対照群に比較して12.5および62.5 mg/kg群の雌雄、0.5および2.5 mg/kg群の雄で肝臓絶対重量が高値あるいは高値傾向を示した。62.5 mg/kg群の雄では腎臓絶対重量が高値を示した。

器官重量/体重比では、対照群に比較して12.5および62.5 mg/kg群の雌雄、0.5および12.5 mg/kg群の雄で肝

臓相対重量が高値を示した。また、62.5 mg/kg群の雄で腎臓相対重量が高値を示した。その他、62.5 mg/kg群の雌で脳および副腎の相対重量が低値を示したが絶対重量に差がみられなかった。また、0.5 mg/kg群の雌で腎臓相対重量が低値を示したが、用量に依存した変化ではなかった。

[回復期間終了時]

対照群に比較して62.5 mg/kg群の雌雄で肝臓絶対重量が高値を示した。その他、雄で精巣上体絶対重量が低値を示したが、この群の体重の低値に起因するものであった。

器官重量/体重比では、対照群に比較して62.5 mg/kg群の雌雄で肝臓相対重量が高値を示した。62.5 mg/kg群の雄で心臓および腎臓の相対重量が高値を示した。

8. 病理学検査

1) 剖検所見 (Table 5)

[投与期間終了時]

肝臓の肥大が0.5 mg/kg以上の群の雄および12.5 mg/kg以上の群の雌で増加した。また、肝臓の白色斑/区域が2.5 mg/kg以上の群の雄と62.5 mg/kg群の雌に観察された。その他に観察された所見は各投与群に散発性または単発性であった。

[回復期間終了時]

肝臓の肥大が62.5 mg/kg群の雄5例、雌2例に認められた。肝臓の褐色化が62.5 mg/kg群の雄5例に認められた。肝臓の赤色斑/区域および白色斑/区域が62.5 mg/kg群の雄にそれぞれ1および2例に観察された。その他に観察された所見は、対照群および62.5 mg/kg群に散発性または単発性であった。

2) 組織所見 (Table 6)

[投与期間終了時]

被験物質によると考えられる所見として、心臓の心筋変性が12.5 mg/kg以上の群の雌雄に、細胞浸潤が0.5 mg/kg以上の群の雄および62.5 mg/kg群の雌に、心筋肥大が12.5 mg/kg以上の群の雌雄に、脾臓の髄外造血が2.5 mg/kg以上の群の雄に、肝臓の小葉辺縁部の肝細胞の空胞変性が2.5 mg/kg以上の群の雄および62.5 mg/kg群の雌に、巣状壊死が2.5 mg/kg以上の群の雄に、肝細胞肥大が0.5 mg/kg以上の群の雄および12.5 mg/kg以上の群の雌に、分裂像増多が62.5 mg/kg群の雄および12.5 mg/kg以上の群の雌に、胆管増殖が0.5 mg/kg以上の群の雄および62.5 mg/kg群の雌に、腎臓の尿管好塩基化の程度の増強が62.5 mg/kg群の雌に、管腔拡張が62.5 mg/kg群の雌に、集合管の尿管管上皮肥大が12.5 mg/kg以上の群の雄および62.5 mg/kg群の雌に、甲状腺の濾胞細胞増生が62.5 mg/kg群の雌雄にそれぞれ観察された。その他、肝臓において色素沈着および好酸性細胞質内封入体が62.5 mg/kg群の雄に、肉芽形成が2.5 mg/kg群の雄に、髄外造血が12.5 mg/kg群

の雄でそれぞれ1例に観察された。一方、雄の対照群および雌の対照群と12.5 mg/kg群に認められた肝細胞の脂肪化は、0.5 mg/kg以上の群の雄および62.5 mg/kg群の雌では観察されなかった。また、雄の腎臓で近位尿管の硝子滴が対照群および0.5 mg/kg群で認められたが、2.5 mg/kg以上の群では認められなかった。

その他の所見は用量に依存しないか、対照群も含めて観察されたか、少数例あるいは散発性的のものであった。

[回復期間終了時]

以下に示す投与終了時に観察されたと同様の所見が62.5 mg/kg群に観察された。心臓の心筋変性および細胞浸潤が雄に、脾臓の髄外造血が雄に、肝臓の肝細胞肥大および巣状壊死が雌雄に、肝細胞の空胞変性および胆管増生が雄に、甲状腺の濾胞細胞増生が雄にそれぞれ認められた。また少数例ではあるが肝臓の色素沈着が雌雄で、好酸性細胞質内封入体、肉芽形成および髄外造血が雄に認められた。一方、62.5 mg/kg群の雄では対照群で観察された肝臓の脂肪化および腎臓の近位尿管の硝子滴が認められなかった。

その他の所見は対照群と62.5 mg/kg群に観察されるものか、少数例あるいは散発性的のものであった。

考察

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールを0, 0.5, 2.5, 12.5および62.5 mg/kgの用量で雌雄のCrj:CD(SD)IGS系ラットに28日間にわたって強制経口投与し、その後、対照群および最高用量群の5匹の動物については投与を休止して14日間の回復期間を設定した。

投与期間および回復期間を通して一般状態に異常は観察されず、対照群を含む各投与群で死亡例も認められなかった。

体重は、各投与群の雌雄において差が認められなかった。

摂餌量は、62.5 mg/kg群の雌雄で高値を示した週がみられ、総摂餌量も高値あるいは高値傾向であった。飼料効率は62.5 mg/kg群の雄で低値を示し、投与期間の平均飼料効率も低値であった。

血液学検査では、2.5 mg/kg以上の群の雄でヘマトクリット値、ヘモグロビン量および赤血球数が低値を示した。さらに、12.5 mg/kg以上の群の雄でMCHCが低値を示した。また、62.5 mg/kg群の雄では血小板数が高値を示しており、いずれも被験物質の影響と考えられた。回復期間終了時にも62.5 mg/kg群の雄でヘマトクリット値、ヘモグロビン量、赤血球数、MCHおよびMCHCが低値、網赤血球比率が高値を示した。また、62.5 mg/kg群の雌雄で血小板数が高値を示しており、休薬しても回復を示さないものと考えられた。

血液凝固能検査では、2.5 mg/kg以上の群の雄および62.5 mg/kg群の雌でフィブリノーゲン量が低値を示し、被験物質の影響と考えられた。回復期間終了時では、

フィブリノーゲン量が62.5 mg/kg群の雌で高値および雄では差がみられなかった。なお、12.5および62.5 mg/kg群の雌ではPTが短縮を示したが、短縮方向への変化であり毒性学的意義のない変化と考えられた。

血液生化学検査では、後述するALT、ASTおよびALPの活性増加が認められた。その他に、2.5 mg/kg以上の群の雄および62.5 mg/kg群の雌で血糖値、62.5 mg/kg群の雌で総コレステロールおよび中性脂肪の濃度がいずれも高値を示した。さらに、12.5 mg/kg以上の群の雄でアルブミン濃度、0.5 mg/kg以上の群の雄および62.5 mg/kg群の雌でA/G比が高値、62.5 mg/kg群の雄で尿素窒素濃度が高値を示した。これらの変化はいずれも被験物質の影響と考えられたがその機序を明らかにすることはできなかった。回復期間終了時には62.5 mg/kg群の雌雄でアルブミン濃度の高値および総ビリルビン濃度が低値を示した。また、雄では尿素窒素濃度、A/G比、ALTおよびALPの活性が、雌では血糖値、総コレステロールおよび総蛋白の濃度がいずれも高値を示し、休薬しても回復を示さないものと考えられた。

器官重量測定では、0.5 mg/kg以上の群の雄および12.5 mg/kg以上の群の雌で肝臓絶対重量が高値あるいは高値傾向を示した。62.5 mg/kg群の雄では腎臓絶対重量が高値を示した。回復期間終了時では62.5 mg/kg群の雌雄で肝臓絶対重量が高値を示した。器官重量/体重比では、0.5 mg/kg以上の群の雄および12.5 mg/kg以上の群の雌で肝臓相対重量が高値を示した。また、62.5 mg/kg群の雄で腎臓相対重量が高値を示した。回復期間終了時では62.5 mg/kg群の雌雄で肝臓相対重量が、雄で腎臓相対重量がいずれも高値を示しており、休薬しても回復を示さないものと考えられた。なお、雄で心臓相対重量が高値を示しており、後述する病理組織学所見と連動するものと考えられた。

病理学検査では、被験物質の影響と考えられる変化として、投与終了時解剖動物において器官重量で肝臓が増加し、肉眼観察で、肝臓の肥大が0.5 mg/kg以上の群の雄および12.5 mg/kg以上の群の雌に、肝臓の白色斑/区域が2.5 mg/kg以上の群の雄および62.5 mg/kg群の雌で観察された。病理組織学所見では、0.5 mg/kg以上の群の雄および12.5 mg/kg以上の群の雌で肝細胞肥大、肝細胞の空胞変性、分裂像増多および胆管増生があり、さらに雄で巣状壊死、肉芽形成、色素沈着および細胞質内封入体が認められた。肝細胞の肥大は壊死、変性などの障害性変化を随伴しており、血液生化学検査ではALT、ALP、ASTの活性の高値が認められたことから、被験物質の肝臓に対する障害性影響が示唆された。2.5 mg/kg以上の群の雄および12.5 mg/kg以上の群の雌で心筋変性、細胞浸潤および心筋肥大が認められた。心筋変性あるいは心筋肥大の発生機序としては被験物質作用の循環動態への影響、心筋への直接作用があると考えられるが^{4,5)}、その病理発生は不明であった。甲状腺の濾胞細胞増生は、肝細胞肥大に示される肝臓の薬物代謝酵素誘導による影響と考えられた^{4,5)}。また、62.5 mg/kg群の雌雄では集合管の尿管管上皮肥大、雄で尿管管好塩

基化および管腔拡張が観察され、尿管の拡張に伴い硝子円柱も一部の動物に認められた。これらの所見の病理発生は不明であったが、被験物質の影響と考えられた。脾臓では髄外造血が2.5 mg/kg以上の群の雄で認められた。血液学検査においてヘマトクリット値、ヘモグロビン量、赤血球数およびMCHCの低下が雄において観察されており、赤血球減少に対する代償性の造血亢進と考えられた。以上の結果からラットにおいては被験物質に対する感受性に性差があり、雄により強い影響が現れることが示唆された。その他の所見は対照群を含め観察され、また散発性または単発性の発生であり、明らかな用量に依存する変化ではないことから自然発生病変と考えられた。

回復終了時の62.5 mg/kg群の雌雄において肝臓の絶対重量および相対重量が増加し、病理組織所見として肝細胞肥大および巣状壊死があり、さらに雄では肝細胞の空胞変性および胆管増成、心臓の心筋変性および細胞浸潤および脾臓の髄外造血、甲状腺の濾胞細胞増生が観察された。しかし、投与終了時解剖例と比較して病変の程度に増強あるいは減弱は認められなかった。以上より、2週間の回復期間では62.5 mg/kg群に明らかな回復性を示す所見はみられなかった。

以上の結果、本試験条件下における2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールの無影響量は、雌では12.5 mg/kg群で肝臓の絶対重量および相対重量の高値、肝臓の肥大、肝細胞肥大が認められたことから2.5 mg/kg/day、また、雄では0.5 mg/kg群で肝臓絶対重量の高値傾向および相対重量の高値、肝臓の肥大、肝細胞肥大が認められたことから0.5 mg/kg/day未満と判断された。

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28日間反復投与毒性試験

Table 1 Hematology of rats treated orally with 2-(2'-hydroxy-3',5'-di-*tert*-butylphenyl)benzotriazole in the twenty-eight-day repeat dose toxicity test

| Item | 28 days dosing groups (mg/kg) | | | | | 14 days recovery groups (mg/kg) | |
|--|-------------------------------|-------------|--------------|--------------|---------------|---------------------------------|--------------|
| | 0 | 0.5 | 2.5 | 12.5 | 62.5 | 0 | 62.5 |
| Male | | | | | | | |
| No. of animals | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| HCT(%) | 45.6 ± 1.8 | 44.6 ± 1.5 | 42.5 ± 2.4* | 41.9 ± 1.2** | 40.7 ± 0.9** | 44.6 ± 1.0 | 40.1 ± 2.7** |
| HGB(g/dL) | 15.2 ± 0.4 | 14.8 ± 0.5 | 13.9 ± 0.8** | 13.6 ± 0.3** | 13.2 ± 0.3** | 15.3 ± 0.3 N | 13.2 ± 0.9** |
| RBC(× 10 ⁶ /mm ³) | 7.89 ± 0.18 | 7.65 ± 0.32 | 7.23 ± 0.33* | 7.18 ± 0.27* | 7.16 ± 0.46** | 8.26 ± 0.16 | 7.65 ± 0.38* |
| MCV(μm ³) | 57.8 ± 1.9 | 58.3 ± 1.5 | 58.7 ± 1.2 | 58.3 ± 1.7 | 57.0 ± 2.7 | 54.0 ± 1.6 | 52.5 ± 2.6 |
| MCH(pg) | 19.3 ± 0.7 | 19.4 ± 0.6 | 19.3 ± 0.4 | 19.0 ± 0.9 | 18.4 ± 0.9 | 18.5 ± 0.5 | 17.3 ± 0.9* |
| MCHC(%) | 33.4 ± 0.7 | 33.2 ± 0.5 | 32.8 ± 0.2 | 32.5 ± 0.7* | 32.3 ± 0.3* | 34.2 ± 0.3 | 32.9 ± 0.6** |
| PLT(× 10 ⁹ /mm ³) | 1202 ± 75 N | 1265 ± 107 | 1280 ± 116 | 1572 ± 430 | 1639 ± 227* | 1196 ± 145 | 1502 ± 134** |
| WBC(× 10 ⁹ /mm ³) | 8.2 ± 2.1 | 6.6 ± 1.8 | 7.5 ± 0.8 | 8.6 ± 3.0 | 8.2 ± 0.8 | 10.8 ± 4.2 | 11.7 ± 4.8 |
| Differential leukocyte counts (%) | | | | | | | |
| NEUT | 11 ± 3 | 16 ± 3 | 13 ± 4 | 15 ± 2 | 13 ± 5 | 9 ± 3 | 12 ± 4 |
| LYMPH | 86 ± 2 | 81 ± 4 | 83 ± 4 | 82 ± 2 | 83 ± 4 | 87 ± 3 | 85 ± 4 |
| MONO | 2 ± 1 | 2 ± 1 | 3 ± 1* | 2 ± 1 | 2 ± 1 | 2 ± 1 | 2 ± 1 |
| EOSN | 1 ± 1 | 1 ± 0 | 0 ± 1 | 1 ± 0 | 1 ± 0 | 1 ± 0 | 1 ± 0 |
| BASO | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 |
| LUC | 1 ± 0 | 1 ± 0 | 1 ± 0 | 1 ± 0 | 1 ± 0 | 1 ± 0 | 1 ± 0 |
| Reticulocyte (%) | 2.8 ± 0.3 | 3.3 ± 0.4 | 3.2 ± 0.3 | 3.9 ± 0.5* | 3.2 ± 1.0 | 2.5 ± 0.4 | 4.4 ± 0.2** |
| PT(sec.) | 17.6 ± 2.4 | 18.0 ± 2.3 | 16.4 ± 1.7 | 15.4 ± 0.9 | 17.5 ± 2.2 | 15.7 ± 1.0 | 16.9 ± 0.5 |
| APTT(sec.) | 24.2 ± 1.3 | 24.0 ± 3.0 | 23.4 ± 2.5 | 20.8 ± 2.1 | 25.4 ± 4.7 | 23.4 ± 1.9 | 20.3 ± 3.5 |
| Fibrinogen (mg/dL) | 249 ± 13 | 224 ± 8 | 189 ± 15** | 198 ± 21** | 193 ± 20** | 240 ± 24 | 214 ± 13 |
| Female | | | | | | | |
| No. of animals | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| HCT(%) | 43.7 ± 1.7 | 43.5 ± 3.1 | 44.0 ± 1.3 | 43.1 ± 1.8 | 41.6 ± 1.6 | 42.2 ± 1.0 | 40.6 ± 1.6 |
| HGB(g/dL) | 15.1 ± 0.9 | 14.9 ± 1.3 | 15.2 ± 0.4 | 14.8 ± 0.7 | 14.1 ± 0.6 | 14.9 ± 0.5 | 14.2 ± 0.6 |
| RBC(× 10 ⁶ /mm ³) | 7.81 ± 0.38 | 7.62 ± 0.61 | 7.79 ± 0.22 | 7.46 ± 0.30 | 7.49 ± 0.30 | 7.80 ± 0.27 | 7.64 ± 0.38 |
| MCV(μm ³) | 56.0 ± 1.1 | 57.1 ± 1.6 | 56.4 ± 0.8 | 57.7 ± 1.4 | 55.6 ± 1.0 | 54.2 ± 0.8 | 53.2 ± 1.8 |
| MCH(pg) | 19.3 ± 0.4 | 19.6 ± 0.6 | 19.5 ± 0.4 | 19.8 ± 0.5 | 18.9 ± 0.4 | 19.1 ± 0.3 | 18.6 ± 0.6 |
| MCHC(%) | 34.5 ± 0.8 | 34.3 ± 0.8 | 34.5 ± 0.4 | 34.4 ± 0.3 | 34.0 ± 0.4 | 35.2 ± 0.3 | 35.1 ± 0.4 |
| PLT(× 10 ⁹ /mm ³) | 1295 ± 118 | 1360 ± 155 | 1367 ± 79 | 1368 ± 138 | 1350 ± 194 | 1166 ± 64 | 1410 ± 95** |
| WBC(× 10 ⁹ /mm ³) | 6.1 ± 1.7 | 7.3 ± 2.2 | 8.4 ± 4.5 | 8.4 ± 2.1 | 8.4 ± 2.4 | 6.1 ± 1.4 | 5.6 ± 1.6 |
| Differential leukocyte counts (%) | | | | | | | |
| NEUT | 11 ± 5 N | 17 ± 8 | 17 ± 12 | 10 ± 4 | 8 ± 3 | 13 ± 4 | 10 ± 3 |
| LYMPH | 86 ± 5 N | 79 ± 8 | 80 ± 12 | 86 ± 4 | 88 ± 2 | 82 ± 4 | 87 ± 3 |
| MONO | 1 ± 0 | 2 ± 1 | 2 ± 1 | 1 ± 1 | 2 ± 1 | 2 ± 0 | 2 ± 1 |
| EOSN | 1 ± 0 | 1 ± 1 | 1 ± 1 | 1 ± 0 | 1 ± 0 | 2 ± 0 | 1 ± 1** |
| BASO | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 |
| LUC | 1 ± 0 | 1 ± 0 | 1 ± 0 | 1 ± 0 | 1 ± 0 | 1 ± 0 | 1 ± 0 |
| Reticulocyte (%) | 2.1 ± 0.4 N | 3.5 ± 1.7 | 2.6 ± 0.4 | 2.5 ± 0.2 | 2.4 ± 0.3 | 2.7 ± 0.4 | 2.6 ± 0.3 |
| PT(sec.) | 15.5 ± 0.4 | 15.4 ± 0.7 | 15.2 ± 0.6 | 14.4 ± 0.7* | 14.2 ± 0.3** | 16.5 ± 1.0 | 15.8 ± 1.1 |
| APTT(sec.) | 19.0 ± 0.8 | 18.9 ± 1.5 | 19.2 ± 2.0 | 17.8 ± 1.5 | 19.4 ± 1.5 | 14.3 ± 1.6 | 15.0 ± 2.7 |
| Fibrinogen (mg/dL) | 193 ± 11 N | 222 ± 46 | 186 ± 9 | 184 ± 29 | 155 ± 10* | 210 ± 7 | 241 ± 7** |

NEUT: Neutrophil, LYMPH: Lymphocyte, MONO: Monocyte, EOSN: Eosinophil, BASO: Basophil, LUC: Large unstained cells
 Values are expressed as Mean ± S.D.

Significant difference from control group; **p* ≤ 0.05, ***p* ≤ 0.01

N: Non parametric analysis

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾール

Table 2 Blood chemistry of rats treated orally with 2-(2'-hydroxy-3',5'-di-tert-butylphenyl)benzotriazole in the twenty-eight-day repeat dose toxicity test

| Item | 28 days dosing groups (mg/kg) | | | | | 14 days recovery groups (mg/kg) | |
|----------------------|-------------------------------|---------------|---------------|---------------|---------------|---------------------------------|---------------|
| | 0 | 0.5 | 2.5 | 12.5 | 62.5 | 0 | 62.5 |
| Male | | | | | | | |
| No. of animals | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Glucose (mg/L) | 122 ± 13 | 132 ± 15 | 170 ± 18** | 170 ± 10** | 156 ± 16** | 166 ± 13 | 182 ± 22 |
| T.cholesterol (mg/L) | 59 ± 11 | 46 ± 9 | 45 ± 4 | 49 ± 13 | 52 ± 20 | 62 ± 13 | 55 ± 19 |
| Triglyceride (mg/L) | 25.5 ± 8.4 N | 24.3 ± 4.5 | 34.5 ± 7.1 | 44.8 ± 20.9 | 45.8 ± 12.5 | 68.0 ± 52.0 | 47.5 ± 26.6 |
| BUN (mg/L) | 13.0 ± 2.5 | 12.9 ± 0.5 | 15.5 ± 1.7 | 15.8 ± 1.3 | 17.2 ± 2.4** | 14.5 ± 2.4 | 19.0 ± 1.9* |
| Creatinine (mg/L) | 0.25 ± 0.05 | 0.23 ± 0.03 | 0.22 ± 0.03 | 0.23 ± 0.03 | 0.21 ± 0.05 | 0.25 ± 0.03 | 0.24 ± 0.04 |
| T.bilirubin (mg/L) | 0.03 ± 0.00 | 0.01 ± 0.01** | 0.02 ± 0.01** | 0.03 ± 0.00 | 0.02 ± 0.01 | 0.06 ± 0.02 | 0.02 ± 0.01** |
| T.protein (g/dL) | 5.84 ± 0.34 | 5.52 ± 0.10 | 5.55 ± 0.24 | 5.72 ± 0.22 | 5.86 ± 0.40 | 6.02 ± 0.19 | 5.95 ± 0.49 |
| Albumin (g/dL) | 3.78 ± 0.22 | 3.90 ± 0.17 | 4.06 ± 0.20 | 4.43 ± 0.18** | 4.40 ± 0.41** | 3.75 ± 0.10 N | 4.22 ± 0.45* |
| A/G | 1.85 ± 0.18 | 2.43 ± 0.23* | 2.75 ± 0.29** | 3.47 ± 0.25** | 3.05 ± 0.55** | 1.66 ± 0.11 N | 2.46 ± 0.34** |
| Sodium (mmol/L) | 145.7 ± 0.6 | 145.5 ± 0.8 | 144.1 ± 0.8* | 145.0 ± 0.6 | 144.7 ± 0.9 | 144.1 ± 0.9 | 144.6 ± 1.3 |
| Potassium (mmol/L) | 4.37 ± 0.27 | 4.49 ± 0.23 | 4.71 ± 0.22 | 4.20 ± 0.15 | 4.47 ± 0.22 | 4.56 ± 0.16 | 4.85 ± 0.41 |
| Chloride (mmol/L) | 108.9 ± 0.9 | 109.1 ± 1.2 | 108.3 ± 1.5 | 108.0 ± 1.2 | 108.5 ± 1.6 | 106.3 ± 1.2 | 106.5 ± 1.0 |
| Calcium (mg/dL) | 10.06 ± 0.24 | 9.85 ± 0.08 | 9.95 ± 0.27 | 10.16 ± 0.25 | 9.84 ± 0.35 | 10.11 ± 0.42 | 10.05 ± 0.29 |
| Lphosphorus (mg/dL) | 8.10 ± 1.03 | 8.24 ± 1.01 | 8.18 ± 0.28 | 8.60 ± 0.52 | 7.82 ± 0.38 | 7.45 ± 0.55 | 8.17 ± 0.54 |
| AST (U/L) | 72 ± 7 N | 71 ± 11 | 65 ± 5 | 83 ± 22 | 115 ± 16* | 61 ± 7 N | 68 ± 22 |
| ALT (U/L) | 30 ± 5 | 28 ± 4 | 32 ± 3 | 42 ± 5* | 48 ± 10** | 25 ± 5 N | 49 ± 29** |
| ALP (U/L) | 757 ± 175 | 992 ± 220 | 1089 ± 168 | 1569 ± 427** | 1462 ± 250** | 622 ± 123 | 906 ± 169* |
| γ-GTP (U/L) | 0.4 ± 0.1 | 0.3 ± 0.1 | 0.3 ± 0.2 | 0.5 ± 0.1 | 0.5 ± 0.1 | 0.5 ± 0.2 | 0.5 ± 0.2 |
| Female | | | | | | | |
| No. of animals | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Glucose (mg/L) | 110 ± 15 | 120 ± 20 | 114 ± 16 | 127 ± 22 | 151 ± 8** | 117 ± 8 | 149 ± 16** |
| T.cholesterol (mg/L) | 49 ± 10 | 59 ± 5 | 50 ± 7 | 54 ± 6 | 84 ± 16** | 63 ± 6 | 91 ± 14** |
| Triglyceride (mg/L) | 12.3 ± 5.6 | 12.1 ± 2.6 | 8.8 ± 3.7 | 12.2 ± 1.1 | 31.9 ± 4.8** | 18.8 ± 7.6 | 37.7 ± 18.8 |
| BUN (mg/L) | 16.1 ± 4.3 | 15.5 ± 1.5 | 16.6 ± 3.8 | 15.8 ± 2.4 | 16.9 ± 1.3 | 16.6 ± 1.2 | 16.8 ± 0.8 |
| Creatinine (mg/L) | 0.30 ± 0.05 | 0.28 ± 0.03 | 0.32 ± 0.07 | 0.30 ± 0.07 | 0.25 ± 0.04 | 0.31 ± 0.02 | 0.30 ± 0.03 |
| T.bilirubin (mg/L) | 0.03 ± 0.01 | 0.03 ± 0.01 | 0.02 ± 0.01 | 0.02 ± 0.01 | 0.01 ± 0.01 | 0.06 ± 0.01 | 0.03 ± 0.01** |
| T.protein (g/dL) | 5.68 ± 0.14 | 5.61 ± 0.18 | 5.53 ± 0.19 | 5.93 ± 0.33 | 5.85 ± 0.19 | 5.91 ± 0.29 | 6.50 ± 0.30* |
| Albumin (g/dL) | 3.81 ± 0.23 | 3.67 ± 0.43 | 3.72 ± 0.12 | 4.12 ± 0.14 | 4.21 ± 0.18 | 3.85 ± 0.32 N | 4.27 ± 0.10* |
| A/G | 2.04 ± 0.26 | 1.95 ± 0.44 | 2.09 ± 0.27 | 2.30 ± 0.25 | 2.59 ± 0.29* | 1.89 ± 0.25 | 1.93 ± 0.18 |
| Sodium (mmol/L) | 143.5 ± 0.3 N | 143.6 ± 1.4 | 143.0 ± 0.7 | 143.8 ± 0.5 | 142.5 ± 1.5 | 144.3 ± 0.9 | 143.7 ± 0.8 |
| Potassium (mmol/L) | 4.06 ± 0.11 | 3.98 ± 0.29 | 4.18 ± 0.40 | 4.24 ± 0.26 | 4.14 ± 0.38 | 4.13 ± 0.24 | 4.35 ± 0.32 |
| Chloride (mmol/L) | 110.3 ± 1.2 | 109.6 ± 1.9 | 109.5 ± 1.8 | 109.9 ± 1.9 | 108.6 ± 2.2 | 109.3 ± 2.2 N | 108.1 ± 0.2 |
| Calcium (mg/dL) | 10.06 ± 0.15 | 9.84 ± 0.33 | 9.71 ± 0.20 | 10.19 ± 0.23 | 10.14 ± 0.40 | 9.85 ± 0.31 | 10.14 ± 0.35 |
| Lphosphorus (mg/dL) | 7.15 ± 0.61 | 7.11 ± 0.43 | 7.02 ± 0.76 | 7.62 ± 1.03 | 7.84 ± 1.15 | 6.08 ± 0.66 | 6.08 ± 0.49 |
| AST (U/L) | 68 ± 5 | 69 ± 11 | 66 ± 7 | 68 ± 9 | 76 ± 12 | 66 ± 13 | 85 ± 19 |
| ALT (U/L) | 21 ± 2 | 22 ± 4 | 23 ± 3 | 27 ± 4 | 33 ± 6** | 25 ± 4 N | 36 ± 21 |
| ALP (U/L) | 490 ± 110 | 409 ± 86 | 414 ± 85 | 433 ± 83 | 633 ± 199 | 381 ± 138 | 247 ± 63 |
| γ-GTP (U/L) | 0.5 ± 0.1 | 0.6 ± 0.2 | 0.4 ± 0.2 | 0.5 ± 0.1 | 0.4 ± 0.1 | 0.8 ± 0.3 | 0.6 ± 0.1 |

Values are expressed as Mean ± S.D.

Significant difference from control group; * $p \leq 0.05$, ** $p \leq 0.01$

N: Non parametric analysis

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Table 3 Urinalysis of rats treated orally with 2-(2'-hydroxy-3',5'-di-*tert*-butylphenyl)benzotriazole in the twenty-eight-day repeat dose toxicity test

| Item | 28 days dosing groups (mg/kg) | | | | | 14 days recovery groups (mg/kg) | |
|------------------------|-------------------------------|------------|------------|------------|------------|---------------------------------|------------|
| | 0 | 0.5 | 2.5 | 12.5 | 62.5 | 0 | 62.5 |
| Male | | | | | | | |
| No. of animals | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Volume (mL) | 7.5 ± 1.6 | 11.8 ± 6.1 | 9.6 ± 4.3 | 10.6 ± 2.1 | 11.5 ± 3.7 | 11.6 ± 4.1 | 9.8 ± 2.1 |
| Osmotic pressure | 1916 ± 170 | 1656 ± 513 | 2085 ± 455 | 2088 ± 220 | 2111 ± 406 | 2201 ± 420 | 2252 ± 170 |
| Color | Slight yellow | 4 | 4 | 3 | 4 | 4 | 5 |
| | Yellow-brown | 1 | 1 | 2 | 1 | 1 | 0 |
| pH | 7 | 0 | 0 | 0 | 1 | 1 | 1 |
| | 7.5 | 2 | 0 | 0 | 1 | 2 | 0 |
| | 8 | 0 | 0 | 2 | 1 | 1 | 0 |
| | 8.5 | 1 | 5 | 3 | 1 | 1 | 4 |
| | ≥9 | 2 | 0 | 0 | 1 | 0 | 0 |
| Occult Blood | - | 3 | 3 | 2 | 5 | 2 | 4 |
| | +/- | 2 | 2 | 2 | 0 | 1 | 1 |
| | 1+ | 0 | 0 | 1 | 0 | 1 | 0 |
| | 3+ | 0 | 0 | 0 | 0 | 1 | 0 |
| Ketones | - | 2 | 0 | 0 | 0 | 0 | 0 |
| | +/- | 1 | 2 | 1 | 0 | 2 | 1 |
| | 1+ | 1 | 2 | 3 | 5 | 3 | 4 |
| | 2+ | 1 | 1 | 1 | 0 | 0 | 0 |
| Glucose (g/dL) | - | 4 | 4 | 3 | 5 | 3 | 5 |
| | 0.1 | 1 | 1 | 2 | 0 | 2 | 0 |
| | Protein +/- | 1 | 0 | 0 | 0 | 0 | 0 |
| | (mg/dL) 30 | 1 | 3 | 0 | 2 | 1 | 0 |
| 100 | 1 | 1 | 2 | 1 | 2 | 5 | |
| ≥300 | 2 | 1 | 3 | 2 | 2 | 0 | |
| Bilirubin | - | 2 | 1 | 1 | 0 | 0 | 3 |
| | 1+ | 1 | 3 | 2 | 2 | 3 | 2 |
| | 2+ | 2 | 1 | 2 | 3 | 2 | 0 |
| Urobilinogen (E.U./dL) | 0.1 | 3 | 4 | 2 | 2 | 2 | 4 |
| | 1.0 | 2 | 1 | 3 | 3 | 3 | 1 |
| Erythrocytes | - | 5 | 5 | 5 | 5 | 4 | 5 |
| | 2+ | 0 | 0 | 0 | 0 | 1 | 0 |
| Leukocytes | - | 5 | 5 | 5 | 5 | 5 | 5 |
| Epith. Cells | - | 5 | 5 | 5 | 5 | 5 | 5 |
| Casts | - | 5 | 5 | 5 | 5 | 5 | 5 |
| Fat glob. | - | 5 | 5 | 5 | 5 | 5 | 5 |
| M. threads | - | 4 | 2 | 4 | 1 | 2 | 3 |
| Others | + | 1 | 3 | 1 | 4 | 3 | 2 |
| | + | 5 | 5 | 5 | 5 | 5 | 5 |

Epith. Cells: Epithelium cells, Fat glob.: Fat globule, M. threads: Mucous threads, Other: Crystals
 Values of volume and osmotic pressure are expressed as Mean ± S.D., the other values are expressed as No. of animals
 Significant difference from control group: * $p \leq 0.05$, ** $p \leq 0.01$

Table 3 (Continued)

| Item | 28 days dosing groups (mg/kg) | | | | | 14 days recovery groups (mg/kg) | |
|------------------------|-------------------------------|------------|-------------|------------|------------|---------------------------------|------------|
| | 0 | 0.5 | 2.5 | 12.5 | 62.5 | 0 | 62.5 |
| Female | | | | | | | |
| No. of animals | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Volume (mL) | 74 ± 4.4 | 11.1 ± 2.6 | 14.6 ± 4.7* | 8.9 ± 1.9 | 8.1 ± 2.8 | 13.4 ± 7.0 | 11.6 ± 6.8 |
| Osmotic pressure | 1983 ± 639 | 1465 ± 389 | 1138 ± 429* | 1697 ± 267 | 2023 ± 490 | 1681 ± 518 | 1912 ± 688 |
| Color | Slight yellow | 5 | 5 | 5 | 5 | 4 | 5 |
| | Yellow-brown | 0 | 0 | 0 | 0 | 1 | 0 |
| pH | 6.5 | 0 | 1 | 0 | 0 | 0 | 0 |
| | 7 | 2 | 0 | 2 | 0 | 0 | 0 |
| | 7.5 | 0 | 0 | 1 | 0 | 1 | 0 |
| | 8 | 2 | 1 | 2 | 1 | 1 | 0 |
| | 8.5 | 1 | 3 | 0 | 4 | 3 | 4 |
| Occult Blood | - | 3 | 4 | 3 | 3 | 2 | 4 |
| | +/- | 2 | 0 | 2 | 2 | 3 | 1 |
| | 1+ | 0 | 1 | 0 | 0 | 0 | 0 |
| stones | - | 2 | 0 | 3 | 0 | 0 | 1 |
| | +/- | 2 | 3 | 1 | 5 | 4 | 4 |
| | 1+ | 1 | 2 | 1 | 0 | 1 | 0 |
| Glucose (g/dL) | - | 3 | 4 | 5 | 4 | 5 | 5 |
| | 0.1 | 2 | 1 | 0 | 1 | 0 | 0 |
| Protein (mg/dL) | - | 1 | 0 | 1 | 0 | 0 | 0 |
| | +/- | 1 | 0 | 1 | 0 | 0 | 1 |
| | 30 | 1 | 3 | 1 | 2 | 0 | 0 |
| | 100 | 0 | 1 | 1 | 2 | 3 | 4 |
| Bilirubin | ≥300 | 2 | 1 | 1 | 1 | 2 | 0 |
| | - | 2 | 1 | 3 | 1 | 2 | 4 |
| | 1+ | 1 | 3 | 2 | 3 | 1 | 1 |
| Urobilinogen (E.U./dL) | 0.1 | 2 | 1 | 0 | 1 | 2 | 0 |
| | 1.0 | 3 | 3 | 3 | 4 | 4 | 1 |
| Erythrocytes | - | 2 | 2 | 2 | 1 | 1 | 4 |
| Leukocytes | - | 5 | 5 | 5 | 5 | 5 | 5 |
| Epith. Cells | - | 5 | 5 | 5 | 5 | 5 | 5 |
| Casts | - | 5 | 5 | 5 | 5 | 5 | 5 |
| Fat glob. | - | 5 | 5 | 5 | 5 | 5 | 5 |
| M. threads | - | 5 | 5 | 5 | 5 | 5 | 5 |
| | + | 4 | 3 | 4 | 4 | 3 | 5 |
| Others | - | 1 | 2 | 1 | 1 | 2 | 0 |
| | + | 0 | 0 | 1 | 0 | 0 | 0 |
| | | 5 | 5 | 4 | 5 | 5 | 5 |

Epith. Cells: Epithelium cells, Fat glob.: Fat globule, M. threads: Mucous threads, Other: Crystals
 Values of volume and osmotic pressure are expressed as Mean ± S.D., the other values are expressed as No. of animals
 Significant difference from control group; * $p \leq 0.05$, ** $p \leq 0.01$

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Table 4 Absolute and relative organ weights of rats treated orally with 2-(2'-hydroxy-3',5'-di-*tert*-butylphenyl) benzotriazole in the twenty-eight-day repeat dose toxicity test

| Item | 28 days dosing groups(mg/kg) | | | | | 14 days recovery groups(mg/kg) | |
|------------------------------|------------------------------|----------------|----------------|-----------------|-----------------|--------------------------------|-----------------|
| | 0 | 0.5 | 2.5 | 12.5 | 62.5 | 0 | 62.5 |
| Male | | | | | | | |
| No. of animals | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Body weight (g) | 323 ± 12 | 328 ± 29 | 338 ± 45 | 332 ± 22 | 329 ± 31 | 402 ± 40 | 357 ± 30 |
| Absolute organ weight | | | | | | | |
| Brain (g) | 2.02 ± 0.08 | 2.03 ± 0.07 | 2.12 ± 0.06 | 2.08 ± 0.05 | 2.06 ± 0.09 | 2.10 ± 0.10 | 2.07 ± 0.10 |
| Heart (g) | 1.09 ± 0.09 | 1.10 ± 0.11 | 1.17 ± 0.14 | 1.18 ± 0.07 | 1.23 ± 0.19 | 1.20 ± 0.10 | 1.28 ± 0.16 |
| Liver (g) | 9.40 ± 0.58 N | 11.65 ± 1.90 | 17.11 ± 3.46* | 21.64 ± 2.73* | 24.47 ± 5.06* | 11.80 ± 1.64 | 20.61 ± 3.36** |
| Kidneys (g) | 2.43 ± 0.22 | 2.54 ± 0.17 | 2.74 ± 0.29 | 2.88 ± 0.40 | 3.04 ± 0.45* | 2.83 ± 0.23 | 2.91 ± 0.40 |
| Spleen (g) | 0.61 ± 0.06 | 0.56 ± 0.08 | 0.62 ± 0.10 | 0.62 ± 0.16 | 0.57 ± 0.08 | 0.68 ± 0.11 | 0.68 ± 0.13 |
| Adrenals (mg) | 51 ± 7 | 45 ± 9 | 53 ± 4 | 44 ± 4 | 47 ± 7 | 59 ± 15 | 50 ± 12 |
| Testes (g) | 2.90 ± 0.16 | 2.84 ± 0.12 | 2.88 ± 0.15 | 2.91 ± 0.15 | 2.92 ± 0.14 | 3.13 ± 0.11 | 3.07 ± 0.18 |
| Thyroid (mg) | 17 ± 4 | 17 ± 2 | 21 ± 5 | 21 ± 3 | 21 ± 4 | 23 ± 2 | 22 ± 3 |
| Pituitary (mg) | 11 ± 2 | 12 ± 2 | 13 ± 2 | 12 ± 2 | 13 ± 4 | 11 ± 2 | 12 ± 3 |
| Thymus (mg) | 578 ± 133 | 439 ± 84 | 546 ± 106 | 657 ± 219 | 496 ± 127 | 418 ± 95 | 411 ± 83 |
| Epididymides (mg) | 657 ± 47 N | 649 ± 7 | 630 ± 11 | 636 ± 16 | 623 ± 55 | 917 ± 59 N | 858 ± 15* |
| Relative organ weight | | | | | | | |
| Brain (%) | 0.624 ± 0.009 N | 0.622 ± 0.038 | 0.633 ± 0.062 | 0.628 ± 0.044 | 0.630 ± 0.046 | 0.527 ± 0.046 | 0.580 ± 0.034 |
| Heart (%) | 0.337 ± 0.026 | 0.336 ± 0.028 | 0.346 ± 0.011 | 0.355 ± 0.017 | 0.374 ± 0.028 | 0.298 ± 0.008 | 0.356 ± 0.016** |
| Liver (%) | 2.908 ± 0.139 N | 3.533 ± 0.296* | 5.045 ± 0.506* | 6.507 ± 0.536* | 7.413 ± 1.283* | 2.930 ± 0.133 N | 5.746 ± 0.527** |
| Kidneys (%) | 0.753 ± 0.075 | 0.775 ± 0.046 | 0.814 ± 0.053 | 0.855 ± 0.080 | 0.927 ± 0.119** | 0.706 ± 0.046 | 0.814 ± 0.066* |
| Spleen (%) | 0.188 ± 0.015 | 0.169 ± 0.012 | 0.183 ± 0.017 | 0.184 ± 0.038 | 0.173 ± 0.025 | 0.169 ± 0.019 | 0.190 ± 0.023 |
| Adrenals (%) | 0.016 ± 0.002 | 0.014 ± 0.003 | 0.016 ± 0.002 | 0.013 ± 0.002 | 0.014 ± 0.001 | 0.015 ± 0.003 | 0.014 ± 0.003 |
| Testes (%) | 0.901 ± 0.080 | 0.871 ± 0.084 | 0.865 ± 0.121 | 0.879 ± 0.046 | 0.891 ± 0.068 | 0.787 ± 0.099 | 0.861 ± 0.043 |
| Thyroid (%) | 0.005 ± 0.001 | 0.005 ± 0.000 | 0.006 ± 0.001 | 0.006 ± 0.001 | 0.007 ± 0.001 | 0.006 ± 0.001 | 0.006 ± 0.001 |
| Pituitary (%) | 0.004 ± 0.001 | 0.004 ± 0.000 | 0.004 ± 0.001 | 0.004 ± 0.001 | 0.004 ± 0.001 | 0.003 ± 0.001 | 0.003 ± 0.001 |
| Thymus (%) | 0.178 ± 0.039 | 0.134 ± 0.022 | 0.162 ± 0.027 | 0.196 ± 0.056 | 0.150 ± 0.026 | 0.103 ± 0.018 | 0.115 ± 0.017 |
| Epididymides (%) | 0.204 ± 0.019 | 0.199 ± 0.018 | 0.189 ± 0.023 | 0.192 ± 0.011 | 0.190 ± 0.013 | 0.231 ± 0.038 | 0.241 ± 0.018 |
| Female | | | | | | | |
| No. of animals | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Body weight (g) | 209 ± 19 | 217 ± 8 | 216 ± 7 | 222 ± 13 | 226 ± 15 | 239 ± 25 | 244 ± 28 |
| Absolute organ weight | | | | | | | |
| Brain (g) | 1.94 ± 0.10 | 1.92 ± 0.08 | 1.95 ± 0.07 | 1.90 ± 0.12 | 1.90 ± 0.03 | 1.99 ± 0.02 | 1.94 ± 0.05 |
| Heart (g) | 0.75 ± 0.07 | 0.77 ± 0.03 | 0.75 ± 0.02 | 0.78 ± 0.05 | 0.84 ± 0.06* | 0.79 ± 0.04 | 0.87 ± 0.06 |
| Liver (g) | 6.39 ± 0.87 | 6.84 ± 0.63 | 6.73 ± 0.26 | 8.67 ± 1.16** | 12.43 ± 0.89** | 6.80 ± 0.86 | 8.85 ± 0.99** |
| Kidneys (g) | 1.70 ± 0.14 | 1.61 ± 0.08 | 1.71 ± 0.09 | 1.72 ± 0.11 | 1.87 ± 0.19 | 1.77 ± 0.18 | 1.86 ± 0.13 |
| Spleen (g) | 0.46 ± 0.02 | 0.48 ± 0.11 | 0.45 ± 0.05 | 0.47 ± 0.09 | 0.43 ± 0.05 | 0.53 ± 0.06 | 0.49 ± 0.03 |
| Adrenals (mg) | 70 ± 14 N | 66 ± 7 | 64 ± 4 | 66 ± 3 | 56 ± 9 | 67 ± 3 | 72 ± 7 |
| Ovaries (mg) | 87 ± 22 | 96 ± 18 | 82 ± 11 | 97 ± 9 | 89 ± 18 | 88 ± 12 | 101 ± 11 |
| Thyroid (mg) | 18 ± 1 | 16 ± 3 | 17 ± 2 | 19 ± 3 | 19 ± 2 | 21 ± 3 | 21 ± 3 |
| Pituitary (mg) | 14 ± 2 | 15 ± 2 | 13 ± 3 | 12 ± 3 | 15 ± 2 | 14 ± 3 | 14 ± 4 |
| Thymus (mg) | 496 ± 60 | 412 ± 88 | 519 ± 120 | 460 ± 106 | 514 ± 87 | 382 ± 51 | 483 ± 90 |
| Relative organ weight | | | | | | | |
| Brain (%) | 0.931 ± 0.053 | 0.884 ± 0.012 | 0.901 ± 0.052 | 0.857 ± 0.046 | 0.841 ± 0.058* | 0.838 ± 0.086 | 0.802 ± 0.084 |
| Heart (%) | 0.357 ± 0.019 | 0.356 ± 0.008 | 0.348 ± 0.007 | 0.351 ± 0.009 | 0.371 ± 0.024 | 0.333 ± 0.022 | 0.357 ± 0.028 |
| Liver (%) | 3.053 ± 0.178 | 3.146 ± 0.197 | 3.112 ± 0.107 | 3.885 ± 0.324** | 5.497 ± 0.172** | 2.835 ± 0.076 | 3.626 ± 0.117** |
| Kidneys (%) | 0.816 ± 0.057 | 0.742 ± 0.033* | 0.789 ± 0.029 | 0.776 ± 0.040 | 0.827 ± 0.042 | 0.744 ± 0.075 | 0.766 ± 0.070 |
| Spleen (%) | 0.222 ± 0.017 | 0.218 ± 0.041 | 0.210 ± 0.033 | 0.209 ± 0.033 | 0.190 ± 0.023 | 0.224 ± 0.037 | 0.203 ± 0.022 |
| Adrenals (%) | 0.033 ± 0.005 | 0.030 ± 0.003 | 0.030 ± 0.002 | 0.030 ± 0.001 | 0.025 ± 0.003** | 0.028 ± 0.004 | 0.030 ± 0.003 |
| Ovaries (%) | 0.041 ± 0.007 | 0.044 ± 0.008 | 0.038 ± 0.005 | 0.044 ± 0.005 | 0.039 ± 0.008 | 0.037 ± 0.004 | 0.041 ± 0.003 |
| Thyroid (%) | 0.009 ± 0.001 | 0.007 ± 0.001 | 0.008 ± 0.001 | 0.008 ± 0.001 | 0.009 ± 0.001 | 0.009 ± 0.002 | 0.008 ± 0.001 |
| Pituitary (%) | 0.007 ± 0.001 | 0.007 ± 0.001 | 0.006 ± 0.001 | 0.006 ± 0.001 | 0.007 ± 0.001 | 0.006 ± 0.001 | 0.006 ± 0.001 |
| Thymus (%) | 0.239 ± 0.035 | 0.191 ± 0.045 | 0.240 ± 0.055 | 0.205 ± 0.039 | 0.227 ± 0.031 | 0.160 ± 0.020 | 0.199 ± 0.038 |

Values are expressed as Mean ± S.D.

Significant difference from control group; * $p \leq 0.05$, ** $p \leq 0.01$.

N: Non parametric analysis

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾール

Table 5 Summary of gross findings of rats treated orally with 2-(2'-hydroxy-3',5'-di-tert-butylphenyl)benzotriazole in the twenty-eight-day repeat dose toxicity test

| Organ | Findings | 28 days dosing groups (mg/kg) | | | | | 14 days recovery groups (mg/kg) | |
|-----------------------------|----------------------------|-------------------------------|-----|-----|------|------|---------------------------------|------|
| | | 0 | 0.5 | 2.5 | 12.5 | 62.5 | 0 | 62.5 |
| Male | | | | | | | | |
| | No. of animals necropsied | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| RESPIRATORY SYSTEM | | | | | | | | |
| lung | brown patch/zone | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| DIGESTIVE SYSTEM | | | | | | | | |
| stomach | black patch/zone | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | white patch/zone | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| liver | brown | 0 | 0 | 0 | 0 | 0 | 0 | 5** |
| | brown patch/zone | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | enlarged | 0 | 2 | 5** | 5** | 5** | 0 | 5** |
| | hepatodiaphragmatic nodule | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | red patch/zone | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| | white patch/zone | 0 | 0 | 2 | 2 | 3 | 0 | 2 |
| URINARY SYSTEM | | | | | | | | |
| kidney | cyst | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | dilated pelvis | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | scarred | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| Female | | | | | | | | |
| | No. of animals necropsied | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| DIGESTIVE SYSTEM | | | | | | | | |
| stomach | black patch/zone | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | white patch/zone | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| liver | enlarged | 0 | 0 | 0 | 3 | 5** | 0 | 2 |
| | red patch/zone | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | white patch/zone | 0 | 0 | 0 | 0 | 3 | 0 | 0 |
| URINARY SYSTEM | | | | | | | | |
| kidney | cyst | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| REPRODUCTIVE SYSTEM | | | | | | | | |
| ovary | cyst | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| uterus | dilated lumen | 1 | 1 | 2 | 0 | 0 | 0 | 0 |
| INTEGUMENTARY SYSTEM | | | | | | | | |
| skin | ulcer | 0 | 1 | 0 | 0 | 0 | 0 | 0 |

Significant difference from control group; * $p \leq 0.05$, ** $p \leq 0.01$

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Table 6 Summary of histopathological findings of rats treated orally with 2-(2'-hydroxy-3',5'-di-tert-butylphenyl) benzotriazole in the twenty-eight-day repeat dose toxicity test

| Organ | Findings | 28 days dosing groups (mg/kg) | | | | | | | | | | | | 14 days recovery groups (mg/kg) | | | | | | | | |
|------------------------------|-----------------------------------|-------------------------------|---|---|-----|---|---|-----|---|---|------|---|---|---------------------------------|---|---|-----|---|---|------|---|---|
| | | 0 | | | 0.5 | | | 2.5 | | | 12.5 | | | 62.5 | | | 0 | | | 62.5 | | |
| | | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| Male | | | | | | | | | | | | | | | | | | | | | | |
| | No. of animals necropsied | 5 | | | 5 | | | 5 | | | 5 | | | 5 | | | 5 | | | 5 | | |
| CARDIOVASCULAR SYSTEM | | | | | | | | | | | | | | | | | | | | | | |
| | heart | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | |
| | degeneration of myocardium | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 |
| | cellular infiltration | 0 | 0 | 0 | 1 | 0 | 0 | 5 | 0 | 0 | 4 | 0 | 0 | 4 | 0 | 0 | 1 | 0 | 0 | 3 | 0 | 0 |
| | hypertrophy, myocardium | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| HEMATOPOIETIC SYSTEM | | | | | | | | | | | | | | | | | | | | | | |
| | spleen | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | |
| | deposit, pigment | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 0 | 0 |
| | hematopoiesis, extramedullary | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 2 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 |
| | lymph node | (5) | | | (0) | | | (0) | | | (0) | | | (5) | | | (0) | | | (0) | | |
| | dilatation, sinus | 1 | 0 | 0 | - | - | - | - | - | - | - | - | - | 0 | 0 | 0 | - | - | - | - | - | - |
| | thymus | (5) | | | (0) | | | (0) | | | (0) | | | (5) | | | (5) | | | (5) | | |
| | Kuersteiner's duct/cyst | 0 | 0 | 0 | - | - | - | - | - | - | - | - | - | 2 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| RESPIRATORY SYSTEM | | | | | | | | | | | | | | | | | | | | | | |
| | lung | (5) | | | (0) | | | (0) | | | (0) | | | (5) | | | (5) | | | (5) | | |
| | accumulation of foamy cells | 1 | 0 | 0 | - | - | - | - | - | - | - | - | - | 3 | 0 | 0 | 1 | 0 | 0 | 4 | 0 | 0 |
| | hypertrophy, media, artery | 1 | 0 | 0 | - | - | - | - | - | - | - | - | - | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| DIGESTIVE SYSTEM | | | | | | | | | | | | | | | | | | | | | | |
| | stomach | (5) | | | (0) | | | (0) | | | (0) | | | (5) | | | (5) | | | (5) | | |
| | dilatation, gland | 0 | 0 | 0 | - | - | - | - | - | - | - | - | - | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| | microgranuloma | 0 | 0 | 0 | - | - | - | - | - | - | - | - | - | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | exocrine pancreas | (5) | | | (0) | | | (0) | | | (0) | | | (5) | | | (5) | | | (5) | | |
| | degeneration, vacuolar | 0 | 0 | 0 | - | - | - | - | - | - | - | - | - | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | rectum | (5) | | | (0) | | | (0) | | | (0) | | | (5) | | | (5) | | | (5) | | |
| | microgranuloma | 0 | 0 | 0 | - | - | - | - | - | - | - | - | - | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| | liver | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | |
| | degeneration, vacuolar | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 |
| | deposit, pigment | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| | fatty change | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 0 |
| | inclusion body, intracytoplasmic | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | necrosis, focal | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 |
| | cellular infiltration, lymphocyte | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | granulation | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | microgranuloma | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 |
| | hematopoiesis, extramedullary | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | hypertrophy, hepatocyte | 0 | 0 | 0 | 3 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | increase in mitosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 |
| | proliferation, bile duct | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 4 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 |
| | foci/area of cellular alteration | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| URINARY SYSTEM | | | | | | | | | | | | | | | | | | | | | | |
| | kidney | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | |
| | basophilic tubules | 2 | 0 | 0 | 3 | 0 | 0 | 4 | 0 | 0 | 3 | 0 | 0 | 3 | 2 | 0 | 4 | 0 | 0 | 4 | 0 | 0 |
| | cast, hyaline | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| | dilatation, tubules | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | hyaline droplet | 2 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| | mineralization | 2 | 0 | 0 | 1 | 0 | 0 | 3 | 0 | 0 | 2 | 0 | 0 | 2 | 0 | 0 | 2 | 0 | 0 | 3 | 0 | 0 |
| | cellular infiltration, lymphocyte | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| | dilatation, renal pelvis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | hypertrophy, tubular epithelium | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | fibrosis, scar | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |

Grade of histopathological finding; 1:slight, 2:moderate, 3:marked
 Numbers in parenthesis indicate No. of animals examined microscopically at this site.
 -:Not examined

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾール

Table 6 (Continued)

| Organ | Findings | 28 days dosing groups (mg/kg) | | | | | | | | | | | | | | | 14 days recovery groups (mg/kg) | | | | | |
|---------------------|-----------------------------------|-------------------------------|---|---|-----|-----|-----|-----|-----|-----|------|-----|-----|------|---|---|---------------------------------|---|---|------|---|---|
| | | 0 | | | 0.5 | | | 2.5 | | | 12.5 | | | 62.5 | | | 0 | | | 62.5 | | |
| | | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| Male | | | | | | | | | | | | | | | | | | | | | | |
| | No. of animals necropsied | 5 | | | 5 | | | 5 | | | 5 | | | 5 | | | 5 | | | 5 | | |
| REPRODUCTIVE SYSTEM | | | | | | | | | | | | | | | | | | | | | | |
| | epididymis | (5) | | | (0) | | | (0) | | | (0) | | | (5) | | | (5) | | | (5) | | |
| | cellular infiltration, lymphocyte | 0 | 0 | 0 | --- | --- | --- | --- | --- | --- | --- | --- | --- | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | prostate | (5) | | | (0) | | | (0) | | | (0) | | | (5) | | | (5) | | | (5) | | |
| | cellular infiltration, lymphocyte | 3 | 0 | 0 | --- | --- | --- | --- | --- | --- | --- | --- | --- | 0 | 0 | 0 | 4 | 0 | 0 | 2 | 0 | 0 |
| ENDOCRINE SYSTEM | | | | | | | | | | | | | | | | | | | | | | |
| | pituitary gland | (5) | | | (0) | | | (0) | | | (0) | | | (5) | | | (5) | | | (5) | | |
| | cyst | 1 | 0 | 0 | --- | --- | --- | --- | --- | --- | --- | --- | --- | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | increase in castration cell | 0 | 0 | 0 | --- | --- | --- | --- | --- | --- | --- | --- | --- | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| | thyroid gland | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | |
| | cellular infiltration, lymphocyte | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | follicular cell hyperplasia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 |
| | ultimobranchial remnant | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 2 | 0 | 0 |
| | adrenal gland | (5) | | | (0) | | | (0) | | | (0) | | | (5) | | | (5) | | | (5) | | |
| | degeneration, vacuolar | 1 | 0 | 0 | --- | --- | --- | --- | --- | --- | --- | --- | --- | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |

Grade of histopathological finding: 1: slight, 2: moderate, 3: marked
 Numbers in parenthesis indicate No. of animals examined microscopically at this site.
 -: Not examined

28日間反復投与毒性試験

Table 6 (Continued)

| Organ | Findings | 28 days dosing groups (mg/kg) | | | | | 14 days recovery groups (mg/kg) | | | | | | | | | | | | | | | | | | |
|--------|-----------------------------------|-------------------------------|---|---|-----|---|---------------------------------|-----|------|---|------|---|---|-----|---|------|-----|---|---|-----|---|---|---|---|---|
| | | 0 | | | 0.5 | | 2.5 | | 12.5 | | 62.5 | | 0 | | | 62.5 | | | | | | | | | |
| | | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | | | | | | |
| Female | No. of animals necropsied | 5 | | | 5 | | | 5 | | | 5 | | | 5 | | | 5 | | | | | | | | |
| | CARDIOVASCULAR SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | |
| | heart | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | | | |
| | degeneration of myocardium | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | cellular infiltration | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | hypertrophy, myocardium | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | HEMATOPOIETIC SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | |
| | spleen | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | | | |
| | deposit, pigment | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 1 | 0 | 0 | 3 | 0 | 0 |
| | microgranuloma | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | hematopoiesis, extramedullary | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | thymus | (5) | | | (0) | | | (0) | | | (0) | | | (5) | | | (5) | | | (5) | | | | | |
| | Kuersteiner's duct/cyst | 0 | 0 | 0 | - | - | - | - | - | - | - | - | - | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | RESPIRATORY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | |
| | lung | (5) | | | (0) | | | (0) | | | (0) | | | (5) | | | (5) | | | (5) | | | | | |
| | accumulation of foamy cells | 1 | 0 | 0 | - | - | - | - | - | - | - | - | - | 2 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | microgranuloma | 1 | 0 | 0 | - | - | - | - | - | - | - | - | - | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | hypertrophy, media, artery | 1 | 0 | 0 | - | - | - | - | - | - | - | - | - | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| | DIGESTIVE SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | |
| | liver | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | | | |
| | degeneration, vacuolar | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | deposit, pigment | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | fatty change | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 4 | 0 | 0 | 4 | 0 | 0 |
| | necrosis, focal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 2 | 0 | 0 |
| | cellular infiltration, lymphocyte | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 2 | 0 | 0 |
| | microgranuloma | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 |
| | hypertrophy, hepatocyte | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 3 | 0 | 0 |
| | increase in mitosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | proliferation, bile duct | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | URINARY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | |
| | kidney | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | | | |
| | basophilic tubules | 1 | 0 | 0 | 2 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 4 | 0 | 0 | 4 | 0 | 0 | 4 | 0 | 0 |
| | cast, hyaline | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | dilatation, tubules | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| | mineralization | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 1 | 0 | 0 | 3 | 0 | 0 | 3 | 0 | 0 | 3 | 0 | 0 |
| | cellular infiltration, lymphocyte | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | hypertrophy, tubular epithelium | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | REPRODUCTIVE SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | |
| | ovary | (5) | | | (0) | | | (0) | | | (0) | | | (5) | | | (5) | | | (5) | | | | | |
| | cyst, brusa | 0 | 0 | 0 | - | - | - | - | - | - | - | - | - | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | deposit, pigment | 0 | 0 | 0 | - | - | - | - | - | - | - | - | - | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| | ENDOCRINE SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | |
| | thyroid gland | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | (5) | | | | | |
| | ectopic thymus | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | follicular cell hyperplasia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | ultimobranchial remnant | 4 | 0 | 0 | 4 | 0 | 0 | 2 | 0 | 0 | 2 | 0 | 0 | 3 | 0 | 0 | 5 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| | adrenal gland | (5) | | | (0) | | | (0) | | | (0) | | | (5) | | | (5) | | | (5) | | | | | |
| | hypertrophy, zona fasciculata | 1 | 0 | 0 | - | - | - | - | - | - | - | - | - | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Grade of histopathological finding: 1:slight, 2:moderate, 3:marked
 Numbers in parenthesis indicate No. of animals examined microscopically at this site.
 -:Not examined

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールの細菌を用いる復帰変異試験

Reverse Mutation Test of 2-(2'-Hydroxy-3',5'-di-tert-butylphenyl)benzotriazole in Bacteria

要約

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールについて細菌を用いる復帰変異試験を実施した。

検定菌として、*Salmonella typhimurium* TA100, TA1535, TA98, TA1537^{uvrA}および*Escherichia coli* WP2 *uvrAの5菌株を用い、S9 mix無添加条件および添加条件のいずれも、用量設定試験で生育阻害が認められなかったことから、本試験はS9 mix無添加条件および添加条件ともに313~5000 µg/plateの範囲で実施した。*

その結果、用いた5種の検定菌のいずれの用量においても、陰性対照値の2倍以上となる復帰変異コロニー数の増加は認められなかった。

以上の結果から2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールは、用いた試験系において変異原性を有しないもの(陰性)と判定した。

方法

1. 被験物質

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールは、淡黄色粉末固体である。用いた被験物質は、ロット番号S4-034-1、純度100% (LC面積百分率)、製造シプロ化成(株)(福井)であり、シプロ化成(株)から供与された。被験物質は、使用時まで室温で保管した。本ロットについては、試験期間中安定であることが確認された。

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールは、ジメチルスルホキシド(DMSO, ロット番号:SEG4422, 和光純薬工業(株))に懸濁して最高用量の調製液を調製した後、同溶媒で所定の濃度に希釈して速やかに試験に用いた。調製時に、発熱、発泡、変色等の変化はみられなかった。

2. 陽性対照物質

用いた陽性対照物質および調製法は以下のとおりである。

各検定菌ごとに用いた陽性対照物質は、当研究所で十分な蓄積データが得られている物質および用量とし、それぞれTable中に示した。

AF2 : 2-(2-フリル)-3-(5-ニトロ-2-フリル)アクリルアミド(和光純薬工業(株))

SA : アジ化ナトリウム(和光純薬工業(株))

9AA : 9-アミノアクリジン(Sigma Chem. Co.)

2AA : 2-アミノアントラセン(和光純薬工業(株))

AF2, 9AAおよび2AAはDMSOに、SAは超純水に溶解したものを-20℃で凍結保存し、解凍後、速やかに試験に用いた。

3. 検定菌

試験には、*Salmonella typhimurium* TA100, TA1535, TA98, TA1537および*Escherichia coli* WP2 *uvrA*を用いた。

*S. typhimurium*の4菌株は1997年8月7日に、*E. coli* WP2 *uvrA*株は1997年4月9日に日本バイオアッセイ研究センターの松島泰次郎博士から分与された。

検定菌は-80℃で凍結保存したものを、各菌株の特性確認は凍結保存菌の調製時に、アミノ酸要求性、UV感受性、膜変異(*rfa*)、アンピシリン耐性因子pKM101(プラスミド)の有無および陰性対照群と陽性対照群の復帰変異コロニー数について調べ、特性が維持されていることを確認した。

試験に際して、ニュートリエントプロスNo. 2(Oxoid Ltd.)を入れたL字型試験管に解凍した種菌を一定量接種し、37℃で10時間往復振とう培養したものを検定菌液とした。

分光光度計により660 nmの吸光度を測定し、検定菌液の増殖を確認した。

4. 培地およびS9 mixの組成

1) 合成培地

培地は、極東製薬工業(株)製の最少グルコース寒天培地を用いた。なお、培地1 Lあたりの組成は下記のとおりである。

| | |
|---------------|--------|
| 硫酸マグネシウム・7水和物 | 0.2 g |
| クエン酸・1水和物 | 2 g |
| リン酸水素二カリウム | 10 g |
| リン酸一アンモニウム | 1.92 g |
| 水酸化ナトリウム | 0.66 g |
| グルコース | 20 g |
| 大洋寒天(清水食品(株)) | 15 g |

径90 mmのシャーレ1枚あたり30 mLを流して固めたものである。

2) トップアガー

下記の水溶液(A)および(B)または(C)を容量比10:1の割合で混合した。

復帰変異試験

- (A) バクトアガー (Difco Lab.) 0.6 w/v%
塩化ナトリウム 0.5 w/v%
- (B) *Salmonella typhimurium* 用
L-ヒスチジン 0.5 mmol/L
D-ピオチン 0.5 mmol/L
- (C) *Escherichia coli* 用
L-トリプトファン 0.5 mmol/L

3) S9 mix

S9 mix 1 mLあたりの組成は下記のとおりである。

| | |
|-----------------------|---------------|
| S9* | 0.1 mL |
| 塩化マグネシウム | 8 μ mol |
| 塩化カリウム | 33 μ mol |
| グルコース-6-リン酸 | 5 μ mol |
| NADH | 4 μ mol |
| NADPH | 4 μ mol |
| ナトリウム-リン酸緩衝液 (pH 7.4) | 100 μ mol |

*:7週齢のSprague-Dawley系雄ラットをフェノバルビタール(PB)および5,6-ベンゾフラボン(BF)の併用投与で酵素誘導して作製したS9(キッコーマン株)を用いた。

5. 試験方法

ブレインキューベーション法⁹⁾により, S9 mix無添加条件および添加条件で試験を行った。

小試験管中に, 被験物質調製液0.1 mL, 0.1 mol/Lナトリウム-リン酸緩衝液(pH 7.4)0.5 mL(S9 mix添加条件においてはS9 mix 0.5 mL), 検定菌液0.1 mLを混合し, 37°Cで20分間ブレインキューベーションしたのち, 約45°Cに保温したトップアガー2 mLを加えて混和し, 合成培地平板上に流して固めた。また, 対照群として被験物質調製液の代わりに使用溶媒, または数種の陽性対照物質溶液を用いた。同時に実施した他試験については, 陰生および陽性対照群を共通とした。

培養は37°Cで48時間行い, 発生した復帰変異コロニー数をコロニーアナライザまたは目視によって算定した。被験物質に由来する沈殿の有無は, 肉眼により確認した。また, 生育阻害の有無については, 肉眼あるいは実体顕微鏡下で, 寒天表面の菌叢の状態から判断した。用いた平板は用量設定試験においては, 陰性および陽性対照群では3枚ずつ, 各用量については1枚ずつとした。また, 本試験においては, 両対照群および各用量につき, 3枚ずつを用い, それぞれの平均値と標準偏差を求めた。

用量設定試験は1回, 本試験は同一用量について2回実施し, 結果の再現性の確認をした。

6. 判定基準

用いた5種の検定菌のうち, 1種以上の検定菌のS9 mix無添加条件あるいはS9 mix添加条件において, 被験物質を含有する平板上における復帰変異コロニー数の平均値が, 陰性対照値の2倍以上に増加し, その増加に再現性および用量依存性が認められた場合に, 当該被験物

質は本試験系において変異原性を有するもの(陽性)と判定することとした。

結果および考察

50.0~5000 μ g/plateの範囲で公比を約3として, 用量設定試験を実施した。その結果, すべての検定菌のS9 mix無添加条件および添加条件のいずれにおいても生育阻害は認められなかった。また, 被験物質に由来する沈殿は, S9 mix無添加条件ではすべての用量で, S9 mix添加条件では150 μ g/plate以上の用量で認められた。

したがって, S9 mix無添加条件および添加条件とも最高用量を5000 μ g/plateとして公比2で5用量を設定して2回の本試験を実施した(Table 1, 2)。その結果, 2回の試験とも陰性対照値の2倍以上となる復帰変異コロニー数の増加は認められなかった。

以上の結果に基づき, 2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールは, 用いた試験系において変異原性を有しないもの(陰性)と判定した。

なお, 2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールは, 当研究所で本試験と並行して実施したチャイニーズ・ハムスター培養細胞を用いる染色体異常試験でも陰性の結果が得られている⁴⁾。また, 関連物質であるブチレチドヒドロキシトルエン⁵⁾については, 復帰変異試験および染色体異常試験で陰性の結果が, p-tert-ブチルフェノール^{6,7)}, 2-tert-ブチルフェノール^{8,9)}および2,4-ジ-tert-ブチルフェノール^{10,11)}については, 復帰変異試験で陰性の, 染色体異常試験で陽性の結果が得られている。

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復帰変異試験

Table 1 Mutagenicity of 2-(2'-hydroxy-3',5'-di-*tert*-butylphenyl) benzotriazole in bacteria (I)

| With(+) or without(-) S9 mix | Test substance dose ($\mu\text{g}/\text{plate}$) | Number of revertants (number of colonies/plate, mean \pm S.D.) | | | | | | | | | | | | | | |
|------------------------------|--|--|-----|-----------------|------------------|-----|-----------------|-----------------|-----|-----------------|-----------------|-----|-----------------|-------------------|-----|-----|
| | | Base-pair substitution type | | | | | | | | | Frameshift type | | | | | |
| | | TA100 | | | TA1535 | | | WP2 <i>uvrA</i> | | | TA98 | | | TA1537 | | |
| S9 mix (-) | 0 | 131 | 123 | 127 | 8 | 12 | 9 | 19 | 23 | 23 | 21 | 26 | 23 | 15 | 12 | 15 |
| | | (127 \pm 4) | | | (10 \pm 2) | | | (22 \pm 2) | | | (23 \pm 3) | | | (14 \pm 2) | | |
| | 313 † | 107 | 105 | 134 | 4 | 12 | 8 | 19 | 19 | 37 | 26 | 15 | 28 | 13 | 6 | 8 |
| | | (115 \pm 16) | | | (8 \pm 4) | | | (25 \pm 10) | | | (23 \pm 7) | | | (9 \pm 4) | | |
| | 625 † | 134 | 116 | 104 | 8 | 9 | 10 | 18 | 15 | 13 | 13 | 14 | 20 | 7 | 10 | 6 |
| | | (118 \pm 15) | | | (9 \pm 1) | | | (15 \pm 3) | | | (16 \pm 4) | | | (8 \pm 2) | | |
| | 1250 † | 123 | 109 | 128 | 5 | 8 | 7 | 16 | 34 | 18 | 20 | 26 | 25 | 8 | 12 | 8 |
| | | (120 \pm 10) | | | (7 \pm 2) | | | (23 \pm 10) | | | (24 \pm 3) | | | (9 \pm 2) | | |
| | 2500 † | 114 | 141 | 137 | 6 | 8 | 11 | 24 | 17 | 17 | 19 | 15 | 14 | 7 | 11 | 15 |
| | | (131 \pm 15) | | | (8 \pm 3) | | | (19 \pm 4) | | | (16 \pm 3) | | | (11 \pm 4) | | |
| | 5000 † | 128 | 118 | 136 | 11 | 14 | 9 | 13 | 23 | 29 | 23 | 21 | 17 | 8 | 7 | 8 |
| | | (127 \pm 9) | | | (11 \pm 3) | | | (22 \pm 8) | | | (20 \pm 3) | | | (8 \pm 1) | | |
| S9 mix (+) | 0 | 122 | 112 | 117 | 12 | 7 | 12 | 37 | 38 | 28 | 17 | 24 | 33 | 15 | 13 | 9 |
| | | (117 \pm 5) | | | (10 \pm 3) | | | (34 \pm 6) | | | (25 \pm 8) | | | (12 \pm 3) | | |
| | 313 † | 101 | 87 | 111 | 8 | 9 | 7 | 20 | 27 | 27 | 28 | 15 | 24 | 8 | 19 | 13 |
| | | (100 \pm 12) | | | (8 \pm 1) | | | (25 \pm 4) | | | (22 \pm 7) | | | (13 \pm 6) | | |
| | 625 † | 102 | 119 | 148 | 11 | 6 | 10 | 27 | 26 | 30 | 19 | 29 | 22 | 8 | 8 | 9 |
| | | (123 \pm 23) | | | (9 \pm 3) | | | (28 \pm 2) | | | (23 \pm 5) | | | (8 \pm 1) | | |
| | 1250 † | 117 | 96 | 107 | 10 | 5 | 5 | 22 | 25 | 30 | 22 | 24 | 26 | 6 | 12 | 10 |
| | | (107 \pm 11) | | | (7 \pm 3) | | | (26 \pm 4) | | | (24 \pm 2) | | | (9 \pm 3) | | |
| | 2500 † | 148 | 132 | 131 | 7 | 16 | 11 | 20 | 22 | 23 | 35 | 24 | 26 | 17 | 10 | 10 |
| | | (137 \pm 10) | | | (11 \pm 5) | | | (22 \pm 2) | | | (28 \pm 6) | | | (12 \pm 4) | | |
| | 5000 † | 139 | 126 | 135 | 11 | 8 | 6 | 29 | 21 | 28 | 26 | 24 | 22 | 12 | 5 | 8 |
| | | (133 \pm 7) | | | (8 \pm 3) | | | (26 \pm 4) | | | (24 \pm 2) | | | (8 \pm 4) | | |
| Positive control S9 mix (-) | Chemical | AF2 ^{a)} | | | SA ^{b)} | | | AF2 | | | AF2 | | | 9AA ^{c)} | | |
| | Dose ($\mu\text{g}/\text{plate}$) | 0.01 | | | 0.5 | | | 0.01 | | | 0.1 | | | 80 | | |
| | Number of colonies/plate | 477 | 501 | 402 | 525 | 546 | 536 | 196 | 209 | 183 | 404 | 417 | 366 | 482 | 343 | 324 |
| | (460 \pm 52) | | | (536 \pm 11) | | | (196 \pm 13) | | | (396 \pm 27) | | | (383 \pm 86) | | | |
| Positive control S9 mix (+) | Chemical | 2AA ^{d)} | | | 2AA | | | 2AA | | | 2AA | | | 2AA | | |
| | Dose ($\mu\text{g}/\text{plate}$) | 1 | | | 2 | | | 10 | | | 0.5 | | | 2 | | |
| | Number of colonies/plate | 770 | 783 | 754 | 391 | 377 | 332 | 938 | 785 | 908 | 487 | 473 | 534 | 258 | 289 | 280 |
| | (769 \pm 15) | | | (367 \pm 31) | | | (877 \pm 81) | | | (498 \pm 32) | | | (276 \pm 16) | | | |

The purity of the test substance was 100 %.

This substance contained 0.01 % water as impurity.

a) 2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide, b) Sodium azide, c) 9-Aminoacridine, d) 2-Aminoanthracene

†: Precipitate was observed on the surface of agar plates.

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾール

Table 2 Mutagenicity of 2-(2'-hydroxy-3',5'-di-tert-butylphenyl)benzotriazole in bacteria (II)

| With (+) or without (-) S9 mix | Test substance dose ($\mu\text{g}/\text{plate}$) | Number of revertants (number of colonies/plate, mean \pm S.D.) | | | | | | | | | | | | | | |
|--------------------------------|--|--|-----|----------------|------------------|-----|----------------|-----------------|-----|----------------|-----------------|----------------|-------------------|-----|-----|-----|
| | | Base-pair substitution type | | | | | | | | | Frameshift type | | | | | |
| | | TA100 | | | TA1535 | | | WP2 <i>uvrA</i> | | | TA98 | | TA1537 | | | |
| S9 mix (-) | 0 | 111 | 125 | 112 | 6 | 11 | 11 | 22 | 29 | 26 | 20 | 21 | 16 | 11 | 11 | 9 |
| | | (116 \pm 8) | | | (9 \pm 3) | | | (26 \pm 4) | | | (19 \pm 3) | | (10 \pm 1) | | | |
| | 313 † | 133 | 113 | 145 | 12 | 8 | 9 | 27 | 28 | 29 | 22 | 15 | 13 | 9 | 5 | 6 |
| | | (130 \pm 16) | | | (10 \pm 2) | | | (28 \pm 1) | | | (17 \pm 5) | | (7 \pm 2) | | | |
| | 625 † | 135 | 127 | 119 | 15 | 16 | 10 | 24 | 24 | 18 | 19 | 19 | 16 | 15 | 10 | 3 |
| | | (127 \pm 8) | | | (14 \pm 3) | | | (22 \pm 3) | | | (18 \pm 2) | | (9 \pm 6) | | | |
| | 1250 † | 146 | 149 | 132 | 11 | 12 | 9 | 19 | 23 | 22 | 13 | 21 | 10 | 19 | 6 | 8 |
| | | (142 \pm 9) | | | (11 \pm 2) | | | (21 \pm 2) | | | (15 \pm 6) | | (11 \pm 7) | | | |
| | 2500 † | 137 | 126 | 136 | 5 | 8 | 16 | 28 | 20 | 30 | 15 | 15 | 13 | 5 | 5 | 6 |
| | | (133 \pm 6) | | | (10 \pm 6) | | | (26 \pm 5) | | | (14 \pm 1) | | (5 \pm 1) | | | |
| | 5000 † | 125 | 142 | 146 | 5 | 12 | 10 | 30 | 27 | 17 | 12 | 16 | 14 | 8 | 8 | 7 |
| | | (138 \pm 11) | | | (9 \pm 4) | | | (25 \pm 7) | | | (14 \pm 2) | | (8 \pm 1) | | | |
| S9 mix (+) | 0 | 129 | 136 | 116 | 10 | 6 | 13 | 29 | 24 | 29 | 26 | 22 | 21 | 15 | 6 | 17 |
| | | (127 \pm 10) | | | (10 \pm 4) | | | (27 \pm 3) | | | (23 \pm 3) | | (13 \pm 6) | | | |
| | 313 † | 101 | 125 | 122 | 9 | 14 | 13 | 12 | 27 | 28 | 14 | 18 | 20 | 10 | 6 | 7 |
| | | (116 \pm 13) | | | (12 \pm 3) | | | (22 \pm 9) | | | (17 \pm 3) | | (8 \pm 2) | | | |
| | 625 † | 118 | 126 | 123 | 13 | 9 | 9 | 35 | 20 | 20 | 20 | 23 | 20 | 10 | 5 | 6 |
| | | (122 \pm 4) | | | (10 \pm 2) | | | (25 \pm 9) | | | (21 \pm 2) | | (7 \pm 3) | | | |
| | 1250 † | 128 | 150 | 113 | 12 | 11 | 12 | 32 | 29 | 23 | 18 | 21 | 12 | 6 | 14 | 9 |
| | | (130 \pm 19) | | | (12 \pm 1) | | | (28 \pm 5) | | | (17 \pm 5) | | (10 \pm 4) | | | |
| | 2500 † | 126 | 126 | 133 | 14 | 8 | 9 | 29 | 19 | 26 | 13 | 21 | 18 | 12 | 9 | 12 |
| | | (128 \pm 4) | | | (10 \pm 3) | | | (25 \pm 5) | | | (17 \pm 4) | | (11 \pm 2) | | | |
| | 5000 † | 141 | 135 | 93 | 15 | 17 | 8 | 35 | 37 | 29 | 19 | 17 | 26 | 6 | 9 | 8 |
| | | (123 \pm 26) | | | (13 \pm 5) | | | (34 \pm 4) | | | (21 \pm 5) | | (8 \pm 2) | | | |
| Positive control S9 mix (-) | Chemical | AF2 ^{a)} | | | SA ^{b)} | | | AF2 | | | AF2 | | 9AA ^{c)} | | | |
| | Dose ($\mu\text{g}/\text{plate}$) | 0.01 | | | 0.5 | | | 0.01 | | | 0.1 | | 80 | | | |
| | Number of colonies/plate | 663 | 671 | 621 | 619 | 482 | 540 | 266 | 277 | 259 | 499 | 498 | 429 | 345 | 445 | 294 |
| | (652 \pm 27) | | | (547 \pm 69) | | | (267 \pm 9) | | | (475 \pm 40) | | (361 \pm 77) | | | | |
| Positive control S9 mix (+) | Chemical | 2AA ^{d)} | | | 2AA | | | 2AA | | | 2AA | | 2AA | | | |
| | Dose ($\mu\text{g}/\text{plate}$) | 1 | | | 2 | | | 10 | | | 0.5 | | 2 | | | |
| | Number of colonies/plate | 856 | 765 | 842 | 359 | 368 | 275 | 781 | 848 | 841 | 372 | 451 | 434 | 245 | 339 | 329 |
| | (821 \pm 49) | | | (334 \pm 51) | | | (823 \pm 37) | | | (419 \pm 42) | | (304 \pm 52) | | | | |

The purity of the test substance was 100%.

This substance contained 0.01% water as impurity.

a) 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide, b) Sodium azide, c) 9-Aminoacridine, d) 2-Aminocanthracene

†: Precipitate was observed on the surface of agar plates.

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールの チャイニーズ・ハムスター培養細胞を用いる染色体異常試験

In Vitro Chromosomal Aberration Test of 2-(2'-Hydroxy-3',5'-di-tert-butylphenyl) benzotriazole in Cultured Chinese Hamster Cells

要約

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールの培養細胞に及ぼす細胞遺伝学的影響について、チャイニーズ・ハムスター培養細胞(CHL/IU)を用いて染色体異常試験を実施した。

S9 mix非存在下および存在下の短時間処理(6時間処理後18時間の回復時間)において、3.2 mg/mL(10 mmol/L)の濃度においても細胞増殖抑制は認められなかった。連続処理(24時間処理)でも3.2 mg/mLにおいて50%を越える増殖抑制作用は認められなかった。従って、すべての処理群で3.2 mg/mLを最高濃度とし、公比2で4~5濃度設定した。

染色体分析の結果、S9 mix非存在下および存在下における短時間処理ではいずれの群(0.80~3.2 mg/mL)においても染色体の構造異常の誘発作用および倍数性細胞の誘発作用は認められなかった。

短時間処理で陰性の結果が得られたため、連続処理を行った。その結果、いずれの群(0.80~3.2 mg/mL)においても染色体の構造異常ならびに倍数性細胞の誘発作用は認められなかった。

以上の結果より、本試験条件下で2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールは、染色体異常を誘発しない(陰性)と結論した。

方法

1. 細胞

CHL/IU細胞はチャイニーズ・ハムスター、肺由来で、リサーチ・リソースバンク(JCRB)から入手(1988年2月、入手時:継代4代、現在21代)した。解凍後は継代10代以内で試験に用いた。仔牛血清(CS, Cansera International Inc.)を10 vol%添加したイーグルMEM(日本製薬(株))培養液を用い、CO₂インキュベーター(37 °C, 5% CO₂)内で培養した。

2. S9 mix

S9(キッコーマン(株))は、フェノバルビタールと5,6-ベンゾフラボンに投与した雄Sprague-Dawley系ラットの肝臓から調製したものを購入した。S9 mixは処理培地に10 vol%添加し、各成分の最終濃度はS9 5 vol%, グルコース6リン酸(Sigma Chemical Co.)0.83 mmol/L, β-ニコチンアミドアデニンジヌクレオチドリン酸(オリエンタル酵母工業(株))0.67 mmol/L, MgCl₂ 0.83 mmol/L,

KCl 5.5 mmol/L, HEPES緩衝液(pH7.2)0.67 mmol/Lとした。

3. 被験物質

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾール(ロット番号:S4-034-1, シプロ化成(株)(福井))は、純度100%(水分0.01%を含む)の淡黄色粉末固体であり、常温で安定で、室温で保管した。本物質は水、アセトンおよびDMSOに不溶(50 mg/mL未満)であった。被験物質原体は、試験後の分析によって試験期間中、室温で安定であったことが確認された。

4. 被験物質の調製

被験物質は用時調製して試験に用いた。媒体は0.5 w/v%カルボキシメチルセルロースナトリウム(CMC Na, ロット番号:WTH1105, 和光純薬工業(株))水溶液を用いて原液を調製した。原液を媒体で順次希釈して所定の濃度の被験物質調製液を作製した。被験物質調製液は、すべての試験において培養液の10 vol%になるように加えた。

5. 培養条件

2 × 10⁴個のCHL/IU細胞を、培養液5 mLを入れたディッシュ(径6 cm)に播き、CO₂インキュベーター内で3日間培養した。その後、連続処理では、新鮮培地と交換後、被験物質を加え、24時間処理した。また、短時間処理では、S9 mix非存在下および存在下で6時間処理し、処理終了後新鮮な培養液でさらに18時間培養した。

6. 細胞増殖抑制試験

染色体異常試験に用いる被験物質の処理濃度を決定するため、被験物質の細胞増殖に及ぼす影響を調べた。培養終了後、細胞を10 vol%ホルマリン水溶液で固定し、0.1 w/v%クリスタルバイオレット水溶液で染色した。被験物質のCHL/IU細胞に対する増殖抑制作用は、単層培養細胞密度計(Monocellater[™], オリンパス光学工業(株))を用いて各群の増殖度を計測し、被験物質処理群の媒体対照群に対する細胞増殖の比をもって指標とした。

その結果、S9 mix非存在下および存在下における短時間処理において最高処理濃度の3.2 mg/mL(10 mmol/L)においても細胞増殖抑制は認められなかった(Fig. 1)。連続処理においては弱い増殖抑制作用が認められたが、最高処理濃度の3.2 mg/mLの濃度においても50%を越える増殖抑制作用は認められなかった(Fig.

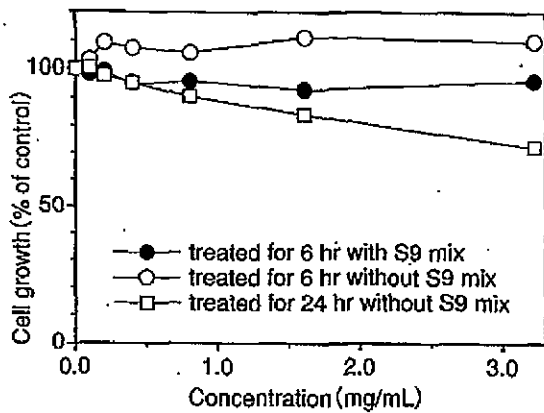


Fig. 1 Growth inhibition of CHL/IU cells treated with 2-(2'-hydroxy-3',5'-di-tert-butylphenyl) benzotriazole. Precipitation was observed at all doses during the treatment.

1).

7. 実験群の設定

細胞増殖抑制試験の結果より、染色体異常試験で用いる被験物質の高濃度群を、すべての処理群において3.2 mg/mL (10 mmol/L) を最高処理濃度とした。短時間処理では、公比2で4濃度群 (0.40~3.2 mg/mL)、連続処理では、公比2で5濃度群 (0.20~3.2 mg/mL) を設定した。

また、陽性対照物質として用いたマイトマイシンC (MC, 協和醗酵工業(株)) およびシクロホスファミド (CP, Sigma Chemical Co.) は、日局注射用水 (株) 大塚製薬工場) に溶解して調製した。それぞれ染色体異常を誘発することが知られている濃度を適用した。

染色体異常試験において、溶媒対照群と処理群では1濃度あたり4枚のディッシュを用いた。このうちの2枚は染色体標本作製し、残りの2枚については単層培養細胞密度計により細胞増殖率を測定した。無処理対照群および陽性対照群については細胞増殖率測定は行わなかった。

8. 染色体標本作製法

培養終了の2時間前に、コルセミドを最終濃度が約0.1 μg/mL になるように培養液に加えた。染色体標本作製は常法に従って行った。スライド標本は各ディッシュにつき6枚作製した。作製した標本は3 vol% ギムザ溶液で染色した。

9. 染色体分析

細胞増殖率測定の結果と分裂指数を細胞毒性の指標として、20%以上の相対増殖率で、かつ2ディッシュともに0.5%以上の分裂指数を示した最も高い濃度を観察対象の最高濃度群とし、観察対象の3濃度群を決定した。その結果 (Table 1~3)、すべての処理系列において観察可能な最高濃度は3.2 mg/mL (10 mmol/L) であったこと

から、この濃度を高濃度群として3濃度群を観察対象とした。

作製したスライド標本のうち、1つのディッシュから得られた異なるスライドを、4名の観察者がそれぞれ処理条件が分からないようにコード化した状態で分析した。染色体の分析は、日本環境変異原学会・哺乳動物試験研究会 (MMS)¹¹⁾ による分類法に基づいて行い、染色体型あるいは染色分体型のギャップ、切断、交換などの構造異常の有無と倍数性細胞 (polyploid) の有無について観察した。また構造異常については1群200個、倍数性細胞については1群800個の分裂中期細胞を分析した。

10. 判定

染色体異常を有する細胞の出現頻度について、溶媒対照群と被験物質処理群および陽性対照群間でフィッシャーの直接確率法¹²⁾ により、有意差検定を実施した ($p < 0.01$)。また、用量依存性に関してコクラン・アーミテッジの傾向性検定¹³⁾ ($p < 0.01$) を行った。これらの検定結果を参考とし、生物学的な観点からの判断を加味して染色体異常誘発性の評価を行った。

結果および考察

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールを加えてS9 mix非存在下および存在下で短時間処理した場合には、いずれの処理群 (0.80, 1.6, 3.2 mg/mL) においても染色体の構造異常および倍数性細胞の有意な増加は認められなかった (Table 1, 2)。

短時間処理で陰性の結果が得られたため、24時間処理を行ったところ、いずれの群 (0.80, 1.6, 3.2 mg/mL) においても染色体の構造異常ならびに倍数性細胞の誘発作用は認められなかった (Table 3)。

陽性対照物質として用いたMCは、S9 mix非存在下で短時間処理および24時間連続処理した場合において染色体の構造異常を誘発し (Table 1, 3)、CPはS9 mix存在下で短時間処理した場合において染色体の構造異常を誘発した (Table 2)。これらの陽性対照物質の結果より、本実験系の成立が確認された。

なお、2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールは、細菌を用いる復帰変異試験において陰性の結果が得られている⁴⁾。また関連物質である2,6-ジ-tert-ブチル-4-メチルフェノール (butylated hydroxytoluene)⁹⁾ については復帰変異試験および染色体異常試験で陰性、*p*-tert-ブチルフェノール^{6,7)}、2-tert-ブチルフェノール^{8,9)} および2,4-ジ-tert-ブチルフェノール^{10,11)} については、復帰変異試験で陰性、染色体異常試験で陽性の結果が報告されている。これらのことから、*tert*-ブチルフェノールの染色体異常誘発活性が、他の置換基が結合することにより失われることが示唆された。

以上の結果より、2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールは、本試験条件下でCHL/IU細胞に染色体異常を誘発しないと結論した。

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2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾール

Table 1 Chromosome analysis of Chinese hamster cells (CHL/IU) treated with 2-(2'-hydroxy-3',5'-di-tert-butylphenyl)benzotriazole (HBBT)** for 6 hr without S9 mix

| Group | Concentration (mg/mL) | S9 mix | Time of exposure (hr) | Concurrent cell growth ^a (%) | Mitotic index ^a (%) | No. of cells analysed | No. of structural aberrations | | | | | | | Total number of cells with aberrations | No. of polyploid cells ^a (%) | Trend test ^b | |
|-----------------------|-----------------------|--------|-----------------------|---|--------------------------------|-----------------------|-------------------------------|-----|-----|-----|-----|------------------|-------|--|---|-------------------------|---------------------|
| | | | | | | | gap | ctb | cte | csb | cse | mul ^a | total | | | | Others ^c |
| Non-treatment | | | | — | — | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0(0.0) | 0(0.0) | 0(0.00) |
| | | | | | | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0(0.0) | 0(0.0) | 0(0.00) |
| | | | | | | 200 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0(0.0) | 0(0.0) | 0(0.00) |
| Negative ^d | 0 | — | 6-(18) | 100.0 | — | 100 | 1 | 0 | 2 | 0 | 0 | 0 | 3 | 0 | 3(3.0) | 2(2.0) | 0(0.00) |
| | | | | | | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0(0.0) | 0(0.0) | 0(0.00) |
| | | | | | | 200 | 1 | 0 | 2 | 0 | 0 | 0 | 3 | 0 | 3(1.5) | 2(1.0) | 0(0.00) |
| HBBT | 0.40† | — | 6-(18) | 107.0 | — | not observed | | | | | | | | | | | |
| HBBT | 0.80† | — | 6-(18) | 111.5 | — | 100 | 0 | 0 | 1 | 1 | 0 | 0 | 2 | 0 | 2(2.0) | 2(2.0) | 0(0.00) |
| | | | | | | 100 | 2 | 0 | 0 | 1 | 0 | 0 | 3 | 0 | 3(3.0) | 1(1.0) | 1(0.25) |
| | | | | | | 200 | 2 | 0 | 1 | 2 | 0 | 0 | 5 | 0 | 5(2.5) | 3(1.5) | 1(0.13) |
| HBBT | 1.6† | — | 6-(18) | 118.5 | — | 100 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1(1.0) | 1(1.0) | 0(0.00) |
| | | | | | | 100 | 0 | 1 | 1 | 0 | 0 | 0 | 2 | 0 | 2(2.0) | 2(2.0) | 1(0.25) |
| | | | | | | 200 | 0 | 1 | 1 | 1 | 0 | 0 | 3 | 0 | 3(1.5) | 3(1.5) | 1(0.13) |
| HBBT | 3.2† | — | 6-(18) | 119.0 | 84, 80 | 100 | 1 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 2(2.0) | 1(1.0) | 1(0.25) |
| | | | | | | 100 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1(1.0) | 0(0.0) | 1(0.25) |
| | | | | | | 200 | 2 | 1 | 0 | 0 | 0 | 0 | 3 | 0 | 3(1.5) | 1(0.5) | 2(0.25) |
| MC | 0.1 (μg/mL) | — | 6-(18) | — | — | 100 | 4 | 34 | 61 | 0 | 1 | 10 | 110 | 0 | 61(61.0) | 59(59.0) | 0(0.00) |
| | | | | | | 100 | 12 | 42 | 66 | 0 | 1 | 0 | 121 | 0 | 68(68.0) | 63(63.0) | 0(0.00) |
| | | | | | | 200 | 16 | 76 | 127 | 0 | 2 | 10 | 231 | 0 | 129(64.5) | 122 ^e (61.0) | 0(0.00) |

Abbreviations: gap: chromatid gap and chromosome gap, ctb: chromatid break, cte: chromatid exchange, csb: chromosome break, cse: chromosome exchange (dicentric and ring), mul: multiple aberrations, TAG: total number of cells with aberrations including gaps, TA: total number of cells with aberrations excluding gaps, MC: mitomycin C.

1) 0.5% Sodium carboxymethylcellulose was used as vehicle and added at the level of 10 vol% per dish. 2) Cell confluency, representing cytotoxicity, was measured with a Monocellater™. 3) Metaphase frequency was calculated by counting 500 cells in each dish. 4) When the number of aberrations in a cell was more than 9, the cell was scored as having 10 aberrations. 5) Others, such as attenuation and premature chromosome condensation, were excluded from the number of structural aberrations. 6) Eight hundred cells were analysed in each group. 7) Cochran-Armitage's trend test was done at $p < 0.01$.

*: Significantly different from the negative control at $p < 0.01$ by Fisher's exact probability test.

** : Purity was 100%, and water (0.01%) was contained as impurity.

† : Precipitation was observed during the treatment.

染色体異常試験

Table 2 Chromosome analysis of Chinese hamster cells (CHL/IU) treated with 2-(2'-hydroxy-3',5'-di-tert-butylphenyl)benzotriazole (HBBT)** for 6 hr with S9 mix

| Group | Concentration (mg/mL) | S9 mix | Time of exposure (hr) | Concurrent cell growth ^a (%) | Mitotic index ^a (%) | No. of cells analysed | No. of structural aberrations | | | | | | | Others ^d | Total number of cells with aberrations | | No. of polyploid cells ^e (%) | Trend test ^g | |
|-----------------------|-----------------------|--------|-----------------------|---|--------------------------------|-----------------------|-------------------------------|-----|-----|-----|-----|------------------|-------|---------------------|--|----------|---|-------------------------|-----|
| | | | | | | | gap | ctb | cte | csb | cse | mul ^h | total | | TAG(%) | TA(%) | | TA | POL |
| Negative ⁱ | 0 | + | 6-(18) | 100.0 | — | 100 | 0 | 2 | 4 | 0 | 0 | 0 | 6 | 0 | 2(2.0) | 2(2.0) | 1(0.25) | | |
| | | | | | | 100 | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 2(2.0) | 0(0.0) | 0(0.00) | | | |
| | | | | | | 200 | 2 | 2 | 4 | 0 | 0 | 8 | 0 | 4(2.0) | 2(1.0) | 1(0.13) | | | |
| HBBT | 0.40† | + | 6-(18) | 98.5 | — | | not observed | | | | | | | | | | | | |
| HBBT | 0.80† | + | 6-(18) | 95.0 | — | 100 | 0 | 1 | 0 | 1 | 0 | 0 | 2 | 0 | 2(2.0) | 2(2.0) | 1(0.25) | | |
| | | | | | | 100 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1(1.0) | 1(1.0) | 0(0.00) | | | |
| | | | | | | 200 | 0 | 1 | 0 | 1 | 1 | 3 | 0 | 3(1.5) | 3(1.5) | 1(0.13) | | | |
| HBBT | 1.6† | + | 6-(18) | 95.5 | — | 100 | 0 | 0 | 1 | 3 | 0 | 0 | 4 | 0 | 2(2.0) | 2(2.0) | 0(0.00) | | |
| | | | | | | 100 | 4 | 1 | 0 | 5 | 0 | 10 | 1 | 6(6.0) | 2(2.0) | 0(0.00) | | | |
| | | | | | | 200 | 4 | 1 | 1 | 8 | 0 | 14 | 1 | 8(4.0) | 4(2.0) | 0(0.00) | | | |
| HBBT | 3.2† | + | 6-(18) | 97.0 | 6.2, 5.6 | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0(0.0) | 0(0.0) | 1(0.25) | | |
| | | | | | | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0(0.0) | 0(0.0) | 0(0.00) | | | |
| | | | | | | 200 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0(0.0) | 0(0.0) | 1(0.13) | | | |
| CP | 5 (µg/mL) | + | 6-(18) | — | — | 100 | 3 | 10 | 23 | 0 | 0 | 0 | 36 | 0 | 30(30.0) | 28(28.0) | 0(0.00) | | |
| | | | | | | 100 | 2 | 19 | 24 | 0 | 0 | 0 | 45 | 0 | 36(36.0) | 34(34.0) | 0(0.00) | | |
| | | | | | | 200 | 5 | 29 | 47 | 0 | 0 | 81 | 0 | 66(33.0) | 62*(31.0) | 0(0.00) | | | |

Abbreviations; gap: chromatid gap and chromosome gap, ctb: chromatid break, cte: chromatid exchange, csb: chromosome break, cse: chromosome exchange (dicentric and ring), mul: multiple aberrations, TAG: total number of cells with aberrations including gaps, TA: total number of cells with aberrations excluding gaps, CP: cyclophosphamide.

1) 0.5 % Sodium carboxymethylcellulose was used as vehicle and added at the level of 10 vol% per dish. 2) Cell confluency, representing cytotoxicity, was measured with a Monocellater™. 3) Metaphase frequency was calculated by counting 500 cells in each dish. 4) When the number of aberrations in a cell was more than 9, the cell was scored as having 10 aberrations. 5) Others, such as attenuation and premature chromosome condensation, were excluded from the number of structural aberrations. 6) Eight hundred cells were analysed in each group. 7) Cochran-Armitage's trend test was done at $p < 0.01$.

*: Significantly different from the negative control at $p < 0.01$ by Fisher's exact probability test.

** : Purity was 100 %, and water (0.01 %) was contained as impurity.

† : Precipitation was observed during the treatment.

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾール

Table 3 Chromosome analysis of Chinese hamster cells (CHL/IU) continuously treated with 2-(2'-hydroxy-3',5'-di-tert-butylphenyl)benzotriazole (HBBT)** for 24 hr without S9 mix

| Group | Concentration (mg/mL) | Time of exposure (hr) | Concurrent cell growth ^a (%) | Mitotic index ^a (%) | No. of cells analysed | No. of structural aberrations | | | | | | | Others ^d | Total number of cells with aberrations | | No. of polyploid cells ^e (%) | Trend test ^f | |
|-----------------------|-----------------------|-----------------------|---|--------------------------------|-----------------------|-------------------------------|-----|-----|-----|-----|------------------|-------|---------------------|--|------------|---|-------------------------|-----|
| | | | | | | gap | ctb | cte | csb | cse | mul ^g | total | | TAG (%) | TA (%) | | TA | POL |
| Non-treatment | | | — | — | 100 | 1 | 0 | 0 | 0 | 0 | 10 | 11 | 0 | 2(2.0) | 1(1.0) | 2(0.50) | | |
| | | | | | 100 | 2 | 1 | 0 | 0 | 0 | 0 | 3 | 0 | 3(3.0) | 1(1.0) | 1(0.25) | | |
| | | | | | 200 | 3 | 1 | 0 | 0 | 0 | 10 | 14 | 0 | 5(2.5) | 2(1.0) | 3(0.38) | | |
| Negative ^h | 0 | 24 | 100.0 | — | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0(0.0) | 0(0.0) | 0(0.00) | | |
| | | | | | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0(0.0) | 0(0.0) | 0(0.00) | | |
| | | | | | 200 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0(0.0) | 0(0.0) | 0(0.00) | | |
| HBBT | 0.20† | 24 | 99.0 | — | | | | | | | | | not observed | | | | | |
| HBBT | 0.40† | 24 | 96.0 | — | | | | | | | | | not observed | | | | | |
| HBBT | 0.80† | 24 | 92.5 | — | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0(0.0) | 0(0.0) | 1(0.25) | | |
| | | | | | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0(0.0) | 0(0.0) | 1(0.25) | | | |
| | | | | | 200 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0(0.0) | 0(0.0) | 2(0.25) | | | |
| HBBT | 1.6† | 24 | 91.5 | — | 100 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1(1.0) | 0(0.0) | 0(0.00) | | |
| | | | | | 100 | 0 | 3 | 0 | 0 | 0 | 0 | 3 | 0 | 3(3.0) | 3(3.0) | 3(0.75) | | |
| | | | | | 200 | 1 | 3 | 0 | 0 | 0 | 0 | 4 | 0 | 4(2.0) | 3(1.5) | 3(0.38) | | |
| HBBT | 3.2† | 24 | 82.5 | 6.8, 6.4 | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0(0.0) | 0(0.0) | 2(0.50) | | |
| | | | | | 100 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1(1.0) | 1(1.0) | 1(0.25) | | |
| | | | | | 200 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1(0.5) | 1(0.5) | 3(0.38) | | |
| MC | 0.05 (μg/mL) | 24 | — | — | 100 | 3 | 19 | 52 | 0 | 0 | 0 | 74 | 1 | 51(51.0) | 48(48.0) | 1(0.25) | | |
| | | | | | 100 | 3 | 26 | 47 | 1 | 0 | 0 | 77 | 0 | 56(56.0) | 54(54.0) | 0(0.00) | | |
| | | | | | 200 | 6 | 45 | 99 | 1 | 0 | 0 | 151 | 1 | 107(53.5) | 102*(51.0) | 1(0.13) | | |

Abbreviations; gap: chromatid gap and chromosome gap, ctb: chromatid break, cte: chromatid exchange, csb: chromosome break, cse: chromosome exchange (dicentric and ring), mul: multiple aberrations, TAG: total number of cells with aberrations including gaps, TA: total number of cells with aberrations excluding gaps, MC: mitomycin C.

1) 0.5% Sodium carboxymethylcellulose was used as vehicle and added at the level of 10 vol% per dish. 2) Cell confluency, representing cytotoxicity, was measured with a Monocellater™. 3) Metaphase frequency was calculated by counting 500 cells in each dish. 4) When the number of aberrations in a cell was more than 9, the cell was scored as having 10 aberrations. 5) Others, such as attenuation and premature chromosome condensation, were excluded from the number of structural aberrations. 6) Eight hundred cells were analysed in each group. 7) Cochran-Armitage's trend test was done at $p < 0.01$.

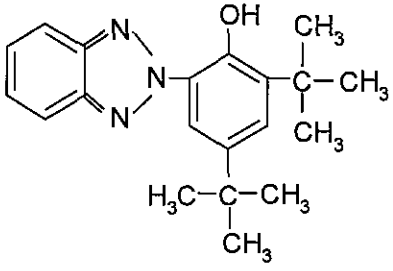
**Significantly different from the negative control at $p < 0.01$ by Fisher's exact probability test.

†Purity was 100%, and water (0.01%) was contained as impurity.

‡Precipitation was observed during the treatment.

17-2. 2-(2H-1,2,3-ベンゾトリアゾール-2-イル)-4,6-ジ-tert-ブチルフェノールの52週間反復投与毒性試験

1. 一般的事項

| 化学物質の名称 (IUPAC命名法による) | 2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾール | | | |
|--------------------------|--|-------------------------|---------------|--|
| 構造式または示性式 |  <p style="text-align: center;">Lot. No. S4-034-1</p> | 分子量(式量) | 323.4 | |
| | | 常温における性状 | 固体 | |
| | | 安定性 (光, 熱, 光など) | 常温で安定 | |
| | | 融点 | 152.0~156.0°C | |
| | | 沸点 | データなし | |
| | | 蒸気圧 | データなし | |
| | | 分配係数 | データなし | |
| 試験に供した 化学物質の純度 | 100 wt% (LC面積法) | 物理 化学 的 性 状 | 溶 水 不溶 | |
| | | | 解 | |
| | | | 度 | |
| 不純物の名称および濃度 | 水分 0.01% (乾燥減量) | | | |

その他 (別紙参照)

- 有害性情報 (急性毒性など)
- その他の物理化学的性質 (pH, pKaなど)
- 溶媒中の安定性
- 取り扱い上の留意点 (危険性, 有害性など)
- 廃棄方法
- 同一性確認のためのIRスペクトル

2. 急性毒性試験

| 試験 No. | 試験の種類および期間 | 動物種 | 1群当たりの動物数 | 投与経路 | 投与量 (mg/kg) | LD ₅₀ 値又はNOEL* (mg/kg) | 実験場所 |
|--------|---|-----|------------|------|-------------------------------------|--|--------|
| 1 | 単回投与毒性試験 | ラット | 雄5匹 雌5匹 | 強制経口 | 2000 | 雌雄 : LD ₅₀ > 2000 mg/kg | 安評センター |
| 2 | 投与量設定試験 (14日間) 観察項目 死亡率 一般状態 体重 摂餌量 臨床検査 器官重量 剖検 | ラット | 雄5匹 雌5匹 | 強制経口 | 0 100 300 1000 | 異常なし ヘマトクリット値, ヘモグロビン量, 赤血球数およびMCHCの低値. 血糖, 中性脂肪, 尿素窒素, アルブミン, A/G, ALPの高値あるいは高値傾向. カリウムの低値. 肝臓の絶対重量および相対重量の高値. 流涎. ヘマトクリット値, ヘモグロビン量, 赤血球数およびMCHCの低値. 血糖, 中性脂肪, 尿素窒素, アルブミン, A/G, ALP, γ-GTP, AST, ALTの高値あるいは高値傾向. カリウムの低値. 肝臓の絶対重量および相対重量の高値. 肝臓の肥大および白色斑/区域. 流涎. ヘマトクリット値, ヘモグロビン量, 赤血球数, MCHCおよびMCVの低値. 血小板数, 白血球数および網状赤血球比率の高値. 血糖, 中性脂肪, 尿素窒素, アルブミン, A/G, ALP, γ-GTP, AST, ALTの高値あるいは高値傾向. カリウムの低値. 肝臓および腎臓の絶対重量および相対重量の高値および高値傾向. 肝臓の肥大および白色斑/区域. | 安評センター |

*NOEL, no-observed-effect level

3. 28日間反復投与毒性試験

| 試験 No. | 試験の種類 および期間 | 動物種 | 1群当りの 動物数 | 投与経路 | 投与量 (mg/kg) | 所見又はNOEL* | 実験場所 |
|--------|--|-----|--------------|------|---------------------------------|--|--------|
| 1 | 投与量設定試験 (28日間) 観察項目 体重 摂餌量 飼料効率 一般状態 臨床検査 器官重量 剖検 病理組織学的検査 | ラット | 雄5匹 | 強制経口 | 0 0.5 2.5 12.5 62.5 | <p>異常なし</p> <p>雄: A/Gの高値. 肝臓の絶対および相対重量の高値あるいは高値傾向. 肝臓の肥大. 肝臓の肝細胞肥大および胆管増殖.</p> <p>雄: ヘマトクリット値, ヘモグロビン量 および赤血球数の低値. フィブリ ノーゲン量の低値. 血糖およびA/Gの高値. 肝臓の絶対および相対重量の高値. 肝臓の肥大および白色斑/区域. 肝臓の肝細胞肥大, 空胞変性, 胆管 増殖, 巣状壊死および肉芽形成. 心 臓の細胞浸潤.</p> <p>雌雄: 肝臓の絶対および相対重量の高値. 肝臓の肥大. 肝臓の肝細胞肥大. 心臓の心筋変性 および心筋肥大.</p> <p>雄: ヘマトクリット値, ヘモグロビン 量, 赤血球数およびMCHCの低値. フィブリノーゲン量の低値. 血糖の高値. アルブミン, A/G, ALT, ALPの高 値. 肝臓の白色斑/区域. 肝臓の空胞変性, 胆管増殖および巣 状壊死. 心臓の細胞浸潤</p> <p>雌: 肝細胞の分裂像増多.</p> <p>雌雄: 摂餌量の高値. 総摂餌量の高値ある いは高値傾向. フィブリノーゲン量の低値. 血糖, A/G, ALTの高値. 肝臓の絶対および相対重量の高値. 肝臓の肥大. 白色斑/区域. 肝臓の肝細胞肥大, 空胞変性, 分裂 像増多および胆管増殖. 心臓の心筋 変性, 細胞浸潤および心筋肥大. 甲 状腺の濾胞細胞増生. 腎臓の尿細管 上皮肥大. <回復試験> アルブミンの高値. 総ビリルビンの 低値. 肝臓の絶対および相対重量の高値. 肝臓の肥大. 肝臓の色素沈着, 巣状壊死および肝 細胞肥大.</p> | 安評センター |

| 試験 No. | 試験の種類 および期間 | 動物種 | 1群当たり の動物数 | 投与経路 | 投与量 (mg/kg) | 所見又はNOEL* | 実験場所 |
|-----------|----------------|-----|---------------|------|----------------|---|------|
| | | | | | 62.5 | <p>雄: 飼料効率および平均飼料効率の低 値。 ヘマトクリット値, ヘモグロビン 量, 赤血球数およびMCHCの低値。 網状赤血球比率の高値。 アルブミン, AST, ALP, 尿素窒素 の高値。 腎臓の絶対および相対重量の高値。 肝臓の肝細胞巣状壊死, 肉芽形成, 色素沈着および細胞質内封入体。腎 臓の尿細管好塩基性化, 間腔拡張お よび硝子円柱。 <回復試験> ヘマトクリット値, ヘモグロビン 量, 赤血球数, MCHおよびMCHCの 低値。網状赤血球比率の高値。 尿素窒素, A/G, ALTおよびALPの 高値。 腎臓の相対重量の高値。 肝臓の褐色化。 肝臓の空胞変性, 細胞質内封入体, 肉芽形成および胆管増殖。心臓の心 筋変性および細胞浸潤。甲状腺の濾 胞細胞増生。</p> <p>雌: 総コレステロールおよび中性脂肪の 高値。 <回復試験> フィブリノーゲン量の高値。 血糖, 総コレステロールおよび総蛋 白の高値</p> <p><u>NOEL</u> 雄 ; < 0.5 mg/kg/day 雌 ; 2.5 mg/kg/dsy</p> | |

*NOEL, no-observed-effect level

4. 52週間反復投与毒性試験

| | | | | | | | | | | | | | | | | |
|------------------|---|---|-----|-----|---|-----|-----|------|----------|---|-----|-----|------|-----|-----|------|
| 被験物質投与期間 | (雄) 自 2003年7月9日 至 2004年7月6日 (雌) 自 2003年7月10日 至 2004年7月7日 | | | | | | | | | | | | | | | |
| 使用動物・系統 | ラット Crj:CD (SD) IGS | | | | 1群当たりの動物数 対照, 低用量, 中間用量, 高用量:雌雄各20匹 | | | | | | | | | | | |
| 投与経路 | 強制経口投与 | | | | 投与13週終了時の検査動物数 対照, 低用量, 中間用量, 高用量/雌雄各10匹 | | | | | | | | | | | |
| 被験物質の純度 | 100% (LC面積法) | | | | 投与52週終了時の検査動物数 対照, 低用量, 中間用量, 高用量/雌雄各10匹 | | | | | | | | | | | |
| 解剖時期 | 投与13週終了時 | | | | | | | | 投与52週終了時 | | | | | | | |
| 群 | 対照 | | 低用量 | | 中間用量 | | 高用量 | | 対照 | | 低用量 | | 中間用量 | | 高用量 | |
| 投与量 (mg/kg) | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 |
| 性別 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 |
| 死亡 ¹⁾ | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 |
| 一般状態 | | | | | | | | | | | | | | | | |
| 胼胝 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 1 | 5 | 1 | 7 | 2 | 2 | 2 |
| 腫脹 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| 活動性低下 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 |
| 赤色尿 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 下腹部汚染 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 腫瘤 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 1 | 0 | 3 |
| 呼吸緩徐 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 |
| 削瘦 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 皮膚蒼白 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 眼球蒼白 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 体温低下 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 腹臥位 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 歯の異常(上顎切歯の歯折) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 0 |
| 脱毛 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 鼻周囲汚染 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 斜傾 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 横臥位 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 呼吸困難 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 体重 | | | | | | | | | | | | | | | | |
| 投与36日 | | | - | | - | | ▽ | | | | | | | | | |
| 投与43-91日 | | | - | | - | | ▼ | | | | | | | | | |
| 投与92-204日 | | | | | | | | | | | | | | | ▽ | |
| 投与232-364日 | | | | | | | | | | | | | | | ▼ | |
| 摂餌量 | | | | | | | | | | | | | | | | |
| 投与8日 | | | - | | △ | | - | | | | | | | | | |
| 投与64日 | | | - | | △ | | - | | | | | | | | | |
| 投与71日 | | | - | | △ | | - | | | | | | | | | |
| 投与78日 | | | - | | ▲ | | - | | | | | | | | | |
| 投与120日 | | | | | | | | | | | | | | | △ | |
| 投与204日 | | | | | | | | | | | | | | | △ | |
| 投与232日 | | | | | | | | | | | | | △ | | ▲ | |
| 投与260-288日 | | | | | | | | | | | | | | | ▲ | |
| 投与344日 | | | | | | | | | ▽ | | | | | | - | |
| 投与364日 | | | | | | | | | | | | | | | ▲ | |

検定結果: -, 有意差なし; △, p<0.05; ▲, p<0.01 (数値: 発現例数).

1) 自然発生性病変に起因した死亡と判断.

| 解剖時期 群 | 投与13週終了時 | | | | | | | | 投与52週終了時 | | | | | | | |
|-----------------------|----------|---|-----|-----|------|-----|-----|------|----------|---|-----|-----|------|-----|-----|------|
| | 対照 | | 低用量 | | 中間用量 | | 高用量 | | 対照 | | 低用量 | | 中間用量 | | 高用量 | |
| | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 |
| 性別 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 |
| 尿検査 | | | | | | | | | | | | | | | | |
| 尿量 | | | - | - | - | - | - | - | | | - | - | - | - | - | △ |
| 尿浸透圧 | | | - | - | - | - | ▲ | - | | | - | - | ▲ | - | △ | ▽ |
| 尿比重 | | | - | - | - | - | ▲ | - | | | - | - | △ | - | - | - |
| 血液学的検査 | | | | | | | | | | | | | | | | |
| 赤血球数 | | | - | - | - | - | ▼ | - | | | - | - | ▽ | - | ▽ | - |
| ヘモグロビン量 | | | - | - | ▽ | - | ▼ | - | | | - | - | - | - | - | - |
| ヘマトクリット値 | | | - | - | ▽ | - | ▼ | ▽ | | | - | - | ↓ | - | ▽ | - |
| MCV | | | - | - | - | - | - | ▼ | | | - | - | - | - | - | - |
| MCHC | | | - | - | - | - | - | △ | | | - | - | - | - | - | - |
| 血小板数 | | | - | - | - | - | △ | - | | | - | - | - | - | ▲ | △ |
| PT | | | - | - | - | - | - | - | | | - | - | - | - | ▲ | - |
| APTT | | | - | - | - | - | - | - | | | - | - | - | - | ↑ | - |
| 非染色性大型細胞数 | | | - | - | △ | - | - | - | | | - | - | - | - | - | - |
| 血液生化学的検査 | | | | | | | | | | | | | | | | |
| 総蛋白質 | | | - | - | - | - | - | △ | | | - | - | - | - | - | - |
| A/G比 | | | - | - | ▲ | - | ▲ | ▲ | | | - | - | ▲ | - | ▲ | ↑ |
| α ₁ -グロブリン | | | - | - | ▼ | - | ▼ | - | | | - | - | ▼ | - | ▼ | ↓ |
| α ₂ -グロブリン | | | - | - | ▼ | - | ▼ | ▽ | | | - | - | ▽ | - | ▼ | ↓ |
| β-グロブリン | | | - | - | ▼ | - | ▼ | ▼ | | | - | - | - | - | ▼ | - |
| アルブミン | | | - | - | ▲ | - | ▲ | ▲ | | | - | - | ▲ | - | ▲ | - |
| 総ビリルビン | | | - | ▽ | - | - | - | ▽ | | | - | - | - | - | - | ▽ |
| アルカリ性フォスファターゼ | | | - | - | ▲ | - | ▲ | ↑ | | | - | - | ▲ | - | ▲ | ▲ |
| グルコース | | | - | - | ▲ | - | ▲ | - | | | - | - | - | - | - | △ |
| 尿素窒素 | | | - | - | △ | - | ▲ | - | | | - | - | - | - | ▲ | - |
| 無機リン | | | - | - | - | - | △ | - | | | - | - | △ | - | - | - |
| ナトリウム | | | - | - | ▽ | - | ▼ | - | | | - | - | - | - | - | - |
| カリウム | | | - | - | ▲ | - | ▲ | - | | | - | - | - | - | - | - |

検定結果: -, 有意差なし; △, p<0.05; ▲, p<0.01; ↑, 傾向.
程度: -, 変化なし; +, 軽度; ++, 中等度; +++, 顕著.

| 解剖時期 | | 投与13週終了時 | | | | | | | | 投与52週終了時 | | | | | | | |
|-------------|------|----------|----|-----|-----|------|-----|-----|------|----------|----|-----|-----|------|-----|-----|------|
| 群 | | 対照 | | 低用量 | | 中間用量 | | 高用量 | | 対照 | | 低用量 | | 中間用量 | | 高用量 | |
| 投与量 (mg/kg) | | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 |
| 性別 | | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 |
| 剖検所見(生存例) | 検査例数 | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 | 10 | 8 | 10 | 10 | 10 | 10 | 9 |
| 肝臓 | | | | | | | | | | | | | | | | | |
| 肥大 | + | 0 | 0 | 0 | 0 | 0 | 0 | 5* | 1 | 0 | 0 | 0 | 0 | 7** | 0 | 9** | 5* |
| 淡灰色斑 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 |
| 暗赤色斑 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| 褪色 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 横隔膜ヘルニア | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| 肺 | | | | | | | | | | | | | | | | | |
| 白色点 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 4 | 0 |
| 暗赤色化 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| 胸腺 | | | | | | | | | | | | | | | | | |
| 暗赤色化 | + | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 小型化 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 8 | 8 | 8 | 10 | 10 | 9 | 9 |
| 膝窩リンパ節 | | | | | | | | | | | | | | | | | |
| 肥大 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| 脾臓 | | | | | | | | | | | | | | | | | |
| 灰白色斑 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 心臓 | | | | | | | | | | | | | | | | | |
| 灰白色化 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| 腎臓 | | | | | | | | | | | | | | | | | |
| 小陥凹 | + | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| 腎盂拡張 | + | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 灰白色腫瘍 | + | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 精巣 | | | | | | | | | | | | | | | | | |
| 小型化 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NA | 0 | NA | 0 | NA | 1 | NA |
| 精巣上体 | | | | | | | | | | | | | | | | | |
| 小型化 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NA | 0 | NA | 0 | NA | 1 | NA |
| 前立腺 | | | | | | | | | | | | | | | | | |
| 暗赤色点 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NA | 0 | NA | 0 | NA | 1 | NA |
| 卵巣 | | | | | | | | | | | | | | | | | |
| 肥大 | + | NA | 0 | NA | 0 | NA | 0 | NA | 0 | NA | 0 | NA | 0 | NA | 2 | NA | 0 |
| 嚢胞 | + | NA | 0 | NA | 0 | NA | 0 | NA | 0 | NA | 2 | NA | 3 | NA | 1 | NA | 2 |
| 卵巣嚢の拡張 | + | NA | 0 | NA | 0 | NA | 0 | NA | 0 | NA | 0 | NA | 0 | NA | 0 | NA | 1 |
| 子宮 | | | | | | | | | | | | | | | | | |
| 内膜ポリープ | + | NA | 0 | NA | 0 | NA | 0 | NA | 0 | NA | 0 | NA | 0 | NA | 0 | NA | 1 |
| 乳腺 | | | | | | | | | | | | | | | | | |
| 乳汁の貯留 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2 | 0 | 3 | 0 | 3 |
| 下垂体 | | | | | | | | | | | | | | | | | |
| 暗赤色点 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 3 | 0 | 1 |
| 肥大 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 2 | 0 | 1 |
| 淡黄色結節 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| 甲状腺 | | | | | | | | | | | | | | | | | |
| 欠損(左側) | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 肥大(右側) | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 副腎 | | | | | | | | | | | | | | | | | |
| 褐色点 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 0 | 1 | 0 | 1 |
| 肥大 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 皮膚 | | | | | | | | | | | | | | | | | |
| 脱毛 | + | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 口頭の白色結節 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| 白色結節 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 灰白色腫瘍 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 1 | 0 | 3 |
| 四肢 | | | | | | | | | | | | | | | | | |
| 後肢の腫脹 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| 後肢の胼胝 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 1 | 5 | 0 | 7 | 2 | 1 | 2 |

検定結果: *, p<0.05; **, p<0.01 (数値: 発現例数).

略号: NA, 非適用.

程度: -, 変化なし; +, 軽度; ++, 中等度; +++, 顕著

| 解剖時期 | | 投与13週終了時 | | | | | | | | 投与13~52週終了時 | | | | | | | |
|-------------|------|----------|---|-----|-----|------|-----|-----|------|-------------|---|-----|-----|------|-----|-----|------|
| 群 | | 対照 | | 低用量 | | 中間用量 | | 高用量 | | 対照 | | 低用量 | | 中間用量 | | 高用量 | |
| 投与量 (mg/kg) | | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 |
| 性別 | | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 |
| 剖検所見(死亡例) | 検査例数 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 |
| 食道 | | | | | | | | | | | | | | | | | |
| 壁の肥厚 | + | | | | | | | 0 | | | | 0 | | | | | 1 |
| 胃 | | | | | | | | | | | | | | | | | |
| 前胃の粘膜肥厚 | + | | | | | | | 0 | | | | 0 | | | | | 1 |
| 前胃の穿孔 | + | | | | | | | 0 | | | | 0 | | | | | 1 |
| 脂肪組織の癒着 | + | | | | | | | 0 | | | | 0 | | | | | 1 |
| 肝臓 | | | | | | | | | | | | | | | | | |
| 褪色 | + | | | | | | | 0 | | | | 1 | | | | | 0 |
| 肺 | | | | | | | | | | | | | | | | | |
| 暗赤色斑 | + | | | | | | | 1 | | | | 0 | | | | | 0 |
| 胸腺 | | | | | | | | | | | | | | | | | |
| 暗赤色点 | + | | | | | | | 1 | | | | 0 | | | | | 0 |
| 小型化 | + | | | | | | | 0 | | | | 2 | | | | | 1 |
| 脾臓 | | | | | | | | | | | | | | | | | |
| 肥大 | + | | | | | | | 0 | | | | 1 | | | | | 0 |
| 腎臓 | | | | | | | | | | | | | | | | | |
| 表面粗造化 | + | | | | | | | 0 | | | | 2 | | | | | 0 |
| 灰白色腫留 | + | | | | | | | 0 | | | | 1 | | | | | 0 |
| 膀胱 | | | | | | | | | | | | | | | | | |
| 赤色尿貯留 | + | | | | | | | 0 | | | | 1 | | | | | 0 |
| 精巣 | | | | | | | | | | | | | | | | | |
| 小型化 | + | | | | | | | 0 | | | | 1 | | | | | NA |
| 乳腺 | | | | | | | | | | | | | | | | | |
| 乳汁貯留 | + | | | | | | | 0 | | | | 0 | | | | | 1 |
| 下垂体 | | | | | | | | | | | | | | | | | |
| 淡赤色腫留 | + | | | | | | | 0 | | | | 0 | | | | | 1 |
| 副腎 | | | | | | | | | | | | | | | | | |
| 肥大 | + | | | | | | | 0 | | | | 1 | | | | | 0 |
| その他 | | | | | | | | | | | | | | | | | |
| 前肢の淡赤色腫留 | + | | | | | | | 0 | | | | 1 | | | | | 0 |

数値: 発現例数

略号: NA, 非適用.

程度: -, 変化なし; +, 軽度; ++, 中等度; +++, 顕著.

| 解剖時期 群 | 投与13週終了時 | | | | | | | | 投与52週終了時 | | | | | | | |
|-------------------|----------|---|-----|-----|------|-----|-----|------|----------|---|-----|-----|------|-----|-----|------|
| | 対照 | | 低用量 | | 中間用量 | | 高用量 | | 対照 | | 低用量 | | 中間用量 | | 高用量 | |
| | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 |
| 性 別 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 |
| 器官重量 (絶対重量) | | | | | | | | | | | | | | | | |
| 最終体重 | | | - | - | - | - | ▼ | - | | | - | - | - | - | ▼ | - |
| 甲状腺 | | | △ | - | - | - | - | - | | | - | - | - | - | - | - |
| 肝臓 | | | - | - | ▲ | - | ▲ | ▲ | | | - | - | ▲ | - | ▲ | ▲ |
| 脾臓 | | | - | ▼ | - | - | - | - | | | - | - | - | - | - | - |
| 副腎 | | | - | - | - | - | ▽ | - | | | - | - | - | - | - | - |
| 精巢上体 | | | - | NA | ▽ | NA | - | NA | | | - | NA | - | NA | - | NA |
| 体重比器官重量 (相対重量) | | | | | | | | | | | | | | | | |
| 脳 | | | - | - | - | - | ▲ | - | | | - | - | - | - | ▲ | - |
| 下垂体 | | | - | - | - | △ | - | - | | | - | - | - | - | ▲ | - |
| 甲状腺 | | | - | - | - | △ | - | - | | | - | - | - | - | △ | - |
| 心臓 | | | - | - | - | - | ▲ | - | | | - | - | - | - | ▲ | - |
| 肺 | | | - | - | - | - | - | - | | | - | - | - | - | ▲ | - |
| 肝臓 | | | - | - | ▲ | - | ▲ | ▲ | | | - | - | ▲ | - | ▲ | ▲ |
| 脾臓 | | | - | ▼ | - | - | - | - | | | - | - | - | - | - | - |
| 腎臓 | | | - | - | - | - | △ | - | | | - | - | - | - | ▲ | - |
| 精巢上体 | | | - | NA | ▽ | NA | - | NA | | | - | NA | - | NA | △ | NA |
| 精巢 | | | - | NA | - | NA | ▲ | NA | | | - | NA | - | NA | ▲ | NA |

検定結果: -, 有意差なし; △, p<0.05; ▲, p<0.01.

略号: NA, 非適用.

| 解剖時期 | | 投与13週終了時 | | | | | | | | 投与13~52週終了時 | | | | | | | |
|-------------|------|----------|----|-----|-----|------|-----|-----|------|-------------|----|-----|-----|------|-----|-----|------|
| 群 | | 対照 | | 低用量 | | 中間用量 | | 高用量 | | 対照 | | 低用量 | | 中間用量 | | 高用量 | |
| 投与量 (mg/kg) | | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 |
| 性別 | | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 |
| 病理組織学的所見 | 検査例数 | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 | 10 | 8 | 10 | 10 | 10 | 10 | 9 |
| (生存例) | | | | | | | | | | | | | | | | | |
| 食道 | | | | | | | | | | | | | | | | | |
| 筋層の繊維化 | + | 1 | 0 | NE | NE | NE | NE | 0 | 1 | 0 | 0 | NE | NE | NE | NE | 0 | 0 |
| 胃 | | | | | | | | | | | | | | | | | |
| 腺胃粘膜の好中球浸潤 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 0 | 1 |
| 腺胃の腺腔拡張 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 1 | 0 | NE | NE | NE | NE | 2 | 0 |
| 盲腸 | | | | | | | | | | | | | | | | | |
| 筋層の繊維化 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 0 | 1 |
| 耳下腺 | | | | | | | | | | | | | | | | | |
| リンパ球浸潤 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 0 | 1 |
| 肝臓 | | | | | | | | | | | | | | | | | |
| 小葉中心部の肝細胞肥大 | + | 0 | 0 | 0 | NE | 3 | 0 | 6 | 6 | 0 | 0 | 0 | NE | 5 | 0 | 7 | 4 |
| | ++ | 0 | 0 | 0 | NE | 0 | 0 | 3 | 0 | 0 | 0 | 0 | NE | 0 | 0 | 1 | 0 |
| | 計 | 0 | 0 | 0 | NE | 3 | 0 | 9** | 6** | 0 | 0 | 0 | NE | 5* | 0 | 8** | 4* |
| 肝細胞への | + | 0 | 0 | 0 | NE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NE | 0 | 0 | 6** | 2 |
| リポフスチン沈着 | | | | | | | | | | | | | | | | | |
| 明細胞性の変異肝細胞巢 | + | 0 | 0 | 0 | NE | 0 | 0 | 0 | 0 | 0 | 0 | 1 | NE | 7 | 0 | 6 | 0 |
| | ++ | 0 | 0 | 0 | NE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NE | 0 | 0 | 1 | 0 |
| | 計 | 0 | 0 | 0 | NE | 0 | 0 | 0 | 0 | 0 | 0 | 1 | NE | 7** | 0 | 7** | 0 |
| 嚢胞状変性 | | | | | | | | | | | | | | | | | |
| 肝細胞の巢状壊死 | + | 0 | 0 | 0 | NE | 0 | 0 | 0 | 0 | 0 | 0 | 2 | NE | 2 | 0 | 4* | 0 |
| 単核細胞浸潤 | + | 1 | 3 | 3 | NE | 2 | 2 | 0 | 1 | 2 | 0 | 2 | NE | 0 | 0 | 3 | 1 |
| 小葉中間帯の | + | 0 | 0 | 1 | NE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NE | 0 | 0 | 0 | 0 |
| 肝細胞脂肪変性 | | | | | | | | | | | | | | | | | |
| 小葉辺縁部の | + | 0 | 1 | 0 | NE | 0 | 0 | 0 | 0 | 1 | 2 | 0 | NE | 0 | 0 | 0 | 0 |
| 肝細胞脂肪変性 | ++ | 0 | 0 | 0 | NE | 0 | 0 | 0 | 0 | 1 | 0 | 2 | NE | 0 | 0 | 0 | 0 |
| | 計 | 0 | 1 | 0 | NE | 0 | 0 | 0 | 0 | 2 | 2 | 2 | NE | 0 | 0 | 0 | 0 |
| 血管拡張 | | | | | | | | | | | | | | | | | |
| 肝細胞腺腫 | + | 0 | 0 | 0 | NE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NE | 0 | 0 | 1 | 0 |
| 好塩基性の変異肝細胞巢 | + | 0 | 0 | 0 | NE | 0 | 0 | 0 | 0 | 0 | 4 | 0 | NE | 0 | 2 | 0 | 2 |
| 髓外造血 | + | 0 | 0 | 0 | NE | 0 | 0 | 0 | 0 | 0 | 2 | 0 | NE | 0 | 0 | 0 | 0 |
| 脾臓 | | | | | | | | | | | | | | | | | |
| 巢状の腺房萎縮 | + | 0 | 1 | NE | NE | NE | NE | 0 | 0 | 0 | 1 | NE | NE | NE | NE | 1 | 0 |
| 巢状の腺房細胞過形成 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 2 | 0 | NE | NE | NE | NE | 3 | 0 |
| ラ氏島の線維化 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 1 | 0 | NE | NE | NE | NE | 0 | 0 |
| リンパ球浸潤 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 0 | 1 |
| 気管 | | | | | | | | | | | | | | | | | |
| 粘膜固有層の好中球浸潤 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 0 | 1 |
| 肺 | | | | | | | | | | | | | | | | | |
| 肺胞内の泡沫細胞集積 | + | 1 | 1 | NE | NE | NE | NE | 3 | 1 | 3 | 4 | NE | NE | NE | NE | 5 | 4 |
| | ++ | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 1 | 0 |
| | 計 | 1 | 1 | NE | NE | NE | NE | 3 | 1 | 3 | 4 | NE | NE | NE | NE | 6 | 4 |
| 肺動脈の鉍質沈着 | + | 1 | 1 | NE | NE | NE | NE | 1 | 2 | 4 | 1 | NE | NE | NE | NE | 5 | 2 |
| 誤嚥性肺炎 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 1 | 0 |
| 胸腺 | | | | | | | | | | | | | | | | | |
| 出血 | + | 0 | 1 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 0 | 0 |
| 萎縮 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 8 | 8 | NE | NE | NE | NE | 9 | 7 |
| | ++ | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 1 | 1 | NE | NE | NE | NE | 0 | 2 |
| | 計 | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 9 | 9 | NE | NE | NE | NE | 9 | 9 |
| 脾臓 | | | | | | | | | | | | | | | | | |
| 被膜肥厚 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 1 | 0 | NE | NE | NE | NE | 0 | 0 |
| 髓外造血 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 2 | NE | NE | NE | NE | 0 | 1 |
| 赤脾髓の褐色色素沈着 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 1 | NE | NE | NE | NE | 0 | 2 |

検定結果: *, p<0.05; **, p<0.01 (数値: 発現例数).

略号: NA, 非適用; NE, 検査せず.

程度: -, 変化なし; +, 軽度; ++, 中等度; +++, 顕著.

| 解剖時期 | 投与13週終了時 | | | | | | | | 投与52週終了時 | | | | | | | | |
|--------------------|----------|----|-----|-----|-----|-----|------|------|----------|----|-----|-----|-----|-----|------|------|-----|
| | 群 | | 対照 | | 低用量 | | 中間用量 | | 高用量 | | 対照 | | 低用量 | | 中間用量 | | 高用量 |
| 投与量 (mg/kg) | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 | |
| 性別 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | |
| 病理組織学的所見 検査例数 | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 | 10 | 8 | 10 | 10 | 10 | 10 | 9 | |
| (生存例-続き) | | | | | | | | | | | | | | | | | |
| 骨髓(胸骨) | | | | | | | | | | | | | | | | | |
| 巢状萎縮 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 0 | 1 |
| 骨髓(大腿) | | | | | | | | | | | | | | | | | |
| 造血亢進 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 1 | 1 | NE | NE | NE | NE | 0 | 0 |
| 巢状萎縮 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 0 | 1 |
| 心臓 | | | | | | | | | | | | | | | | | |
| 単核細胞浸潤 | + | 2 | 0 | NE | NE | NE | NE | 4 | 0 | 3 | 1 | NE | NE | NE | NE | 4 | 2 |
| 心筋層の線維化 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 4 | 0 | NE | NE | NE | NE | 2 | 1 |
| 腎臓 | | | | | | | | | | | | | | | | | |
| 好塩基性尿管 | + | 0 | 0 | NE | NE | NE | NE | 1 | 0 | 4 | 0 | NE | NE | NE | NE | 2 | 2 |
| 皮髓境界部の鉍質沈着 | + | 0 | 1 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 0 | 0 |
| 腎芽腫 | + | 0 | 1 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 0 | 0 |
| 蛋白円柱 | + | 1 | 0 | NE | NE | NE | NE | 0 | 0 | 4 | 0 | NE | NE | NE | NE | 2 | 1 |
| 腎盂の出血 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 1 | 0 | NE | NE | NE | NE | 0 | 0 |
| 皮質の単核細胞浸潤 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 2 | 0 | NE | NE | NE | NE | 1 | 1 |
| 腎盂の単核細胞浸潤 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 2 | 1 | NE | NE | NE | NE | 0 | 0 |
| 皮質の好中球浸潤 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 1 | NE | NE | NE | NE | 0 | 0 |
| 腎盂の好中球浸潤 | + | 0 | 0 | NE | NE | NE | NE | 1 | 0 | 1 | 0 | NE | NE | NE | NE | 0 | 1 |
| 腎盂腔への好中球滲出 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 1 | 1 | NE | NE | NE | NE | 0 | 1 |
| 腎乳頭部の鉍質沈着 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 3 | NE | NE | NE | NE | 2 | 1 |
| 腎盂の鉍質沈着 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 1 | 3 | NE | NE | NE | NE | 0 | 1 |
| 尿管上皮の過形成 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 0 | 1 |
| 腎盂移行上皮の過形成 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 0 | 1 |
| 膀胱 | | | | | | | | | | | | | | | | | |
| 筋層の好中球浸潤 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 1 | 0 | NE | NE | NE | NE | 0 | 0 |
| 精巣 | | | | | | | | | | | | | | | | | |
| 精細管萎縮 | ++ | 0 | NA | NE | NA | NE | NA | 0 | NA | 0 | NA | NE | NA | NE | NA | 1 | NA |
| | +++ | 0 | NA | NE | NA | NE | NA | 0 | NA | 0 | NA | NE | NA | NE | NA | 1 | NA |
| | 計 | 0 | NA | NE | NA | NE | NA | 0 | NA | 0 | NA | NE | NA | NE | NA | 2 | NA |
| ライディッヒ細胞の 巢状過形成 | + | 0 | NA | NE | NA | NE | NA | 0 | NA | 0 | NA | NE | NA | NE | NA | 1 | NA |
| 精巣上体 | | | | | | | | | | | | | | | | | |
| 精子減少 | +++ | 0 | NA | NE | NA | NE | NA | 0 | NA | 0 | NA | NE | NA | NE | NA | 1 | NA |
| 単核細胞浸潤 | + | 0 | NA | NE | NA | NE | NA | 0 | NA | 1 | NA | NE | NA | NE | NA | 0 | NA |
| 前立腺 | | | | | | | | | | | | | | | | | |
| 単核細胞浸潤 | + | 2 | NA | NE | NA | NE | NA | 2 | NA | 1 | NA | NE | NA | NE | NA | 2 | NA |
| 出血 | + | 0 | NA | NE | NA | NE | NA | 0 | NA | 0 | NA | NE | NA | NE | NA | 1 | NA |
| 萎縮 | + | 0 | NA | NE | NA | NE | NA | 0 | NA | 4 | NA | NE | NA | NE | NA | 3 | NA |
| | ++ | 0 | NA | NE | NA | NE | NA | 0 | NA | 0 | NA | NE | NA | NE | NA | 2 | NA |
| | 計 | 0 | NA | NE | NA | NE | NA | 0 | NA | 4 | NA | NE | NA | NE | NA | 5 | NA |
| 卵巢 | | | | | | | | | | | | | | | | | |
| 卵巢囊の拡張 | + | NA | 0 | NA | NE | NA | NE | NA | 0 | NA | 0 | NA | NE | NA | NE | NA | 1 |
| 嚢胞 | + | NA | 0 | NA | NE | NA | NE | NA | 0 | NA | 2 | NA | NE | NA | NE | NA | 2 |
| 子宮 | | | | | | | | | | | | | | | | | |
| 内膜間質ポリープ | + | NA | 0 | NA | NE | NA | NE | NA | 0 | NA | 0 | NA | NE | NA | NE | NA | 1 |
| 子宮腺上皮細胞の 扁平上皮化生 | + | NA | 0 | NA | NE | NA | NE | NA | 0 | NA | 5 | NA | NE | NA | NE | NA | 2 |
| 膣 | | | | | | | | | | | | | | | | | |
| 粘膜の粘液変性 | + | NA | 0 | NA | NE | NA | NE | NA | 0 | NA | 1 | NA | NE | NA | NE | NA | 1 |

検定結果: 各被験物質群で有意差なし(数値: 発現例数).

略号: NA, 非適用; NE, 検査せず.

程度: -, 変化なし; +, 軽度; ++, 中等度; +++, 顕著.

| 解剖時期 | 投与13週終了時 | | | | | | | | 投与52週終了時 | | | | | | | | |
|----------------------|----------|----|-----|-----|-----|-----|------|------|----------|-----|-----|-----|-----|-----|------|------|-----|
| | 群 | | 対照 | | 低用量 | | 中間用量 | | 高用量 | | 対照 | | 低用量 | | 中間用量 | | 高用量 |
| 投与量 (mg/kg) | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 | |
| 性別 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | |
| 病理組織学的所見 (生存例-続き) | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 | 10 | 8 | 10 | 10 | 10 | 10 | 9 | |
| 乳腺 | | | | | | | | | | | | | | | | | |
| 小葉過形成 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 2 | NE | NE | NE | NE | 0 | 4 |
| 腺房/導管の拡張 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 1 | NE | NE | NE | NE | 0 | 2 |
| | ++ | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 2 | NE | NE | NE | NE | 0 | 3 |
| | 計 | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 3 | NE | NE | NE | NE | 0 | 5 |
| 乳腺腫 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 1 | NE | NE | NE | NE | 0 | 1 |
| 線維腺腫 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 2 | NE | NE | NE | NE | 0 | 1 |
| 乳腺癌 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 1 | NE | NE | NE | NE | 0 | 1 |
| 下垂体 | | | | | | | | | | | | | | | | | |
| 前葉の嚢胞 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 1 | 0 |
| 前葉の過形成 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 3 | 3 | NE | NE | NE | NE | 0 | 3 |
| 甲状腺 | | | | | | | | | | | | | | | | | |
| 後鰓体遺残 | + | 0 | 4 | NE | NE | NE | NE | 1 | 2 | 1 | 2 | NE | NE | NE | NE | 1 | 1 |
| 間質への好酸性物質沈着 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 1 | 0 |
| C細胞過形成 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 0 | 1 |
| 副腎 | | | | | | | | | | | | | | | | | |
| 巣状の皮質細胞肥大 | + | 1 | 0 | NE | NE | NE | NE | 1 | 0 | 2 | 2 | NE | NE | NE | NE | 3 | 2 |
| 巣状の皮質細胞過形成 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 1 | 4 | NE | NE | NE | NE | 1 | 1 |
| 血管拡張 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 4 | NE | NE | NE | NE | 0 | 1 |
| 大脳 | | | | | | | | | | | | | | | | | |
| 側脳質拡張 | + | 1 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 0 | 0 |
| ハーダー腺 | | | | | | | | | | | | | | | | | |
| リンパ球浸潤 | + | 0 | 0 | NE | NE | NE | NE | 0 | 0 | 0 | 0 | NE | NE | NE | NE | 0 | 1 |
| その他 | | | | | | | | | | | | | | | | | |
| 胼胝部位(後肢)の潰瘍 | + | NA | NA | NA | NA | NA | NA | NA | NA | 4/5 | 1/1 | NA | NA | NA | NA | 0/1 | 2/2 |
| | ++ | NA | NA | NA | NA | NA | NA | NA | NA | 1/5 | 0/1 | NA | NA | NA | NA | 1/1 | 0/2 |
| | 計 | NA | NA | NA | NA | NA | NA | NA | NA | 5/5 | 1/1 | NA | NA | NA | NA | 1/1 | 2/2 |
| 膝窩リンパ節の 形質細胞増加 | + | NA | NA | NA | NA | NA | NA | NA | NA | 1/1 | NA | NA | NA | NA | NA | 1/1 | NA |

検定結果: 各被験物質群で有意差なし(数値: 発現例数).

略号: NA, 非適用; NE, 検査せず.

程度: -, 変化なし; +, 軽度; ++, 中等度; +++, 顕著.

| 解剖時期 群 | 投与13週終了時 | | | | | | | | 投与13~52週終了時 | | | | | | | |
|------------------|----------|---|-----|-----|------|-----|-----|------|-------------|---|-----|-----|------|-----|-----|------|
| | 対照 | | 低用量 | | 中間用量 | | 高用量 | | 対照 | | 低用量 | | 中間用量 | | 高用量 | |
| 投与量 (mg/kg) | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 |
| 性別 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 |
| 病理組織学的所見 | 検査例数 | | | | | | | | | | | | | | | |
| (死亡例) | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 |
| 食道 | | | | | | | | | | | | | | | | |
| 潰瘍 | | | | | | | 0 | | | | 0 | | | | | 1 |
| 胃 | | | | | | | | | | | | | | | | |
| 腺胃びらん | | | | | | | 0 | | | | 1 | | | | | 0 |
| 前胃穿孔性潰瘍 | | | | | | | 0 | | | | 0 | | | | | 1 |
| 肝臓 | | | | | | | | | | | | | | | | |
| 小葉中心部の肝細胞肥大 | | | | | | | 1 | | | | 0 | | | | | 0 |
| 小葉中心部の 肝細胞空胞化 | | | | | | | 0 | | | | 1 | | | | | 0 |
| 小葉中心部の肝細胞壊死 | | | | | | | 0 | | | | 1 | | | | | 0 |
| 肺 | | | | | | | | | | | | | | | | |
| 出血 | | | | | | | 1 | | | | 0 | | | | | 0 |
| 浮腫 | | | | | | | 1 | | | | 0 | | | | | 0 |
| 肺胞内の泡沫細胞集積 | | | | | | | 0 | | | | 1 | | | | | 0 |
| 胸腺 | | | | | | | | | | | | | | | | |
| 出血 | | | | | | | 1 | | | | 0 | | | | | 0 |
| 萎縮 | | | | | | | 0 | | | | 1 | | | | | 1 |
| | | | | | | | | | | | 1 | | | | | 0 |
| 腸間膜リンパ節 | | | | | | | | | | | | | | | | |
| 萎縮 | | | | | | | 0 | | | | 1 | | | | | 0 |
| 脾臓 | | | | | | | | | | | | | | | | |
| 白脾髄の萎縮 | | | | | | | 0 | | | | 1 | | | | | 1 |
| 髓外造血 | | | | | | | 0 | | | | 2 | | | | | 0 |
| 赤脾髄の褐色色素沈着 | | | | | | | 0 | | | | 0 | | | | | 1 |
| 骨髓(胸骨) | | | | | | | | | | | | | | | | |
| 造血亢進 | | | | | | | 0 | | | | 2 | | | | | 0 |
| 骨髓(大腿) | | | | | | | | | | | | | | | | |
| 造血亢進 | | | | | | | 0 | | | | 2 | | | | | 0 |
| 心臓 | | | | | | | | | | | | | | | | |
| 単核細胞浸潤 | | | | | | | 0 | | | | 1 | | | | | 0 |
| 大動脈 | | | | | | | | | | | | | | | | |
| 中膜の鈣質沈着 | | | | | | | 0 | | | | 1 | | | | | 0 |
| 腎臓 | | | | | | | | | | | | | | | | |
| 皮質の鈣質沈着 | | | | | | | 0 | | | | 1 | | | | | 0 |
| 腎芽腫 | | | | | | | 0 | | | | 1 | | | | | 0 |
| 好塩基性尿細管 | | | | | | | 0 | | | | 1 | | | | | 0 |
| 精巣 | | | | | | | | | | | | | | | | |
| 精細管萎縮 | | | | | | | 0 | | | | 1 | | | | | NA |
| 前立腺 | | | | | | | | | | | | | | | | |
| 前立腺炎 | | | | | | | 0 | | | | 1 | | | | | NA |
| 卵巣 | | | | | | | | | | | | | | | | |
| 萎縮 | | | | | | | NA | | | | NA | | | | | 1 |
| 腔 | | | | | | | | | | | | | | | | |
| 内腔への好中球滲出 | | | | | | | NA | | | | NA | | | | | 1 |
| 乳腺 | | | | | | | | | | | | | | | | |
| 腺房/導管拡張 | | | | | | | 0 | | | | 0 | | | | | 1 |
| 下垂体 | | | | | | | | | | | | | | | | |
| 後葉の嚢胞 | | | | | | | 1 | | | | 0 | | | | | 0 |
| 前葉の腺腫 | | | | | | | 0 | | | | 0 | | | | | 1 |
| 甲状腺 | | | | | | | | | | | | | | | | |
| 後鰓体遺残 | | | | | | | 0 | | | | 1 | | | | | 0 |

数値: 発現例数.

略号: NA, 非適用.

程度: -, 変化なし; +, 軽度; ++, 中等度; +++, 顕著.

| 解剖時期 | 投与13週終了時 | | | | | | | | 投与13～52週終了時 | | | | | | | | |
|----------------------|----------|---|-----|-----|-----|-----|------|------|-------------|---|-----|-----|-----|-----|------|------|-----|
| | 群 | | 対照 | | 低用量 | | 中間用量 | | 高用量 | | 対照 | | 低用量 | | 中間用量 | | 高用量 |
| 投与量 (mg/kg) | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 | 0 | 0 | 0.1 | 0.5 | 0.5 | 2.5 | 2.5 | 12.5 | |
| 性別 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | 雄 | 雌 | |
| 病理組織学的所見 (死亡例-続き) | 検査例数 | | | | | | | | | | | | | | | | |
| 副腎 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 | |
| 束状帯のびまん性の 皮質細胞肥大 | | | | | | | 0 | | | | 1 | | | | | 0 | |
| その他 | | | | | | | | | | | | | | | | | |
| 前肢の横紋筋肉腫 | | | | | | | NE | | | | 1/1 | | | | | NE | |

数値: 発現例数.

略号: NE, 検査せず.

程度: -, 変化なし; +, 軽度; ++, 中等度; +++, 顕著.

| NOEL (mg/kg) | 雄, 0.1 mg/kg | 雌, 2.5 mg/kg |
|----------------|---|--------------|
| NOELの推定根拠とした変化 | <p>雄では, 尿浸透圧と比重の変動, 赤血球系への影響, 血清の蛋白質の変動, 血清のグルコース, ALPとBUNの増加, 肝臓の肥大と重量増加および肝細胞肥大がみられなかった0.1 mg/kgと判断した.</p> <p>雌では, 尿量および尿浸透圧の変動, 血小板数の増加, 血清蛋白質の変動, 血清のグルコースとALPの増加, 肝臓の肥大と淡灰白色斑, 肝臓重量の増加および肝細胞肥大がみられなかった2.5 mg/kgと判断した.</p> <p>なお, 雄の肝臓にみられたリポフスチン沈着, 明細胞性の変異肝細胞巣および嚢胞状変性は, 肝細胞肥大(ペルオキシゾームの増加)に伴う二次的変化と判断した.</p> | |

要約

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールをラットに 13 または 52 週間反復経口投与した。投与量は、雄で 0 (対照群), 0.1, 0.5 および 2.5 mg/kg, 雌で 0 (対照群), 0.5, 2.5 および 12.5 mg/kg とした。

1. 一般状態

投与期間を通して、全例で被験物質投与に起因した変化は認められなかった。

2. 体重

体重の低値が、2.5 mg/kg 群の雄で投与 36 日以降に認められた。

3. 摂餌量

摂餌量の高値が、2.5 mg/kg 群の雄で投与 120 日以降に認められた。

4. 尿検査

投与 13 週時では、尿浸透圧および尿比重の高値が 2.5 mg/kg 群の雄に認められた。

投与 52 週時では、投与 13 週時と同様な変化として、尿浸透圧の高値が 0.5 および 2.5 mg/kg 群の雄に、尿比重の高値が 0.5 mg/kg 群の雄に認められた。投与 13 週時にみられなかった変化として、尿量の高値と本変化に伴う尿浸透圧の低値が 12.5 mg/kg 群の雌に認められた。

5. 血液学的検査

投与 13 週終了時では、血小板数の高値と赤血球数の低値が 2.5 mg/kg 群の雄に、ヘマトクリット値およびヘモグロビン量の低値が 0.5 および 2.5 mg/kg 群の雄に認められた。

投与 52 週終了時では、投与 13 週終了時と同様な変化として、血小板数の高値が 2.5 mg/kg 群の雄と 12.5 mg/kg 群の雌に、赤血球数およびヘマトクリット値の低値ないし低値傾向が 0.5 および 2.5 mg/kg 群の雄に認められた。投与 13 週終了時にみられなかった変化として、PT および APTT の延長ないし延長傾向が 2.5 mg/kg 群の雄に認められた。

6. 血液生化学的検査

投与 13 週終了時では、A/G 比、アルブミン百分比および ALP の高値ないし高値傾向と α_2 -および β -グロブリンの低値が 0.5 および 2.5 mg/kg 群の雄と 12.5 mg/kg 群の雌に、グルコースおよび BUN の高値と α_1 -グロブリンの低値が 0.5 および 2.5 mg/kg 群の雄に、総蛋白質の高値が 12.5 mg/kg 群の雌に認められた。

投与 52 週終了時では、投与 13 週終了時と同様な変化として、A/G 比および ALP の高値ないし高値傾向と α_1 -および α_2 -グロブリンの低値ないし低値傾向が 0.5 および 2.5 mg/kg 群の雄と 12.5 mg/kg 群の雌に、アルブミン百分比の高値が 0.5 および 2.5 mg/kg 群の雄に、BUN の高値と β -グロブリンの低値が 2.5 mg/kg 群の雄に、グルコースの高値が 12.5 mg/kg 群の雌に認められた。

7. 剖検

投与 13 週終了時では、肝臓の肥大が 2.5 mg/kg 群の雄 5 例と 12.5 mg/kg 群の雌 1 例に認められた。

投与 52 週終了時では、投与 13 週終了時と同様な変化として、肝臓の肥大が 0.5 mg/kg 群の雄 7 例、2.5 mg/kg 群の雄 9 例および 12.5 mg/kg 群の雌 5 例に認められた。投与 13 週終了時にみられなかった変化として、肝臓の灰白色斑が 2.5 mg/kg 群の雄 2 例と 12.5 mg/kg 群の雌 1 例に認められた。

8. 器官重量

投与 13 週終了時では、肝臓の絶対および相対重量の高値が 0.5 および 2.5 mg/kg 群の雄と 12.5 mg/kg 群の雌にみられ、腎臓の相対重量の高値が 2.5 mg/kg 群の雄で認められた。

投与 52 週終了時では、投与 13 週終了時と同様な変化として、肝臓の絶対および相対重量の高値が 0.5 および 2.5 mg/kg 群の雄と 12.5 mg/kg 群の雌にみられ、腎臓の相対重量の高値が 2.5 mg/kg 群の雄で認められた。

9. 病理組織学的検査

投与 13 週終了時では、肝臓の小葉中心部の軽度ないし中等度な肝細胞肥大が、雄では 0.5 mg/kg 群の 3 例と 2.5 mg/kg 群の 9 例に、雌では 12.5 mg/kg 群の 6 例に認められた。

投与 52 週終了時では、投与 13 週終了時と同様な変化として、肝臓の小葉中心部の軽度ないし中等度な肝細胞肥大が、雄では 0.5 mg/kg 群の 5 例と 2.5 mg/kg 群の 8 例に、雌では 12.5 mg/kg 群

の4例に認められた。投与13週終了時にみられなかった変化として、肝細胞への軽度なりポフスチン沈着が2.5 mg/kg 群の雄6例と12.5 mg/kg 群の雌2例に、軽度ないし中等度な明細胞性変異肝細胞巣が0.1 mg/kg 群の雄1例と0.5および2.5 mg/kg 群の雄各7例に、軽度な嚢胞状変性が0.1および0.5 mg/kg 群の雄各2例と2.5 mg/kg 群の雄4例に認められた。また、2.5 mg/kg 群の雄では、肝細胞の軽度な巣状壊死の発生頻度が、対照群と比較してやや増加する傾向が認められた（発生頻度：4/10例）。

上述の肝細胞肥大は、小葉中心部にみられていること、かつ肥大した肝細胞の細胞質が好酸性顆粒状を呈していたことから、ペルオキシゾームの増加の可能性が考えられた。また、リポフスチン沈着、明細胞性変異肝細胞巣および嚢胞状変性については、ペルオキシゾームの増加に伴った二次的変化の可能性が推察された。

以上のことから、本試験条件下における2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールの無影響量 (NOEL) は、雄で0.1 mg/kg/day, 雌で2.5 mg/kg/day と判断した。

試験成績

1. 一般状態の観察

観察結果を Table 1, 2 および Appendix 1, 2 に示した.

1) 生存例

被験物質投与に起因したと考えられる変化は認められなかった.

投与期間中に、胼胝 (後肢) が各被験物質群の雌雄に、胼胝に伴う腫脹 (後肢) が 2.5 mg/kg 群の雄に、一過性の歯の異常 (上顎切歯の歯折) が 0.5 mg/kg 群の雄に、腫瘤 (右腋窩部または腹部) が 2.5 および 12.5 mg/kg 群の雌に、脱毛 (頸部から胸部および上腕部から前腕部) が 12.5 mg/kg 群の雌にそれぞれ認められたが、高用量 (雄で 2.5 mg/kg, 雌で 12.5 mg/kg) 群に同様な変化がないか、あるいは対照群と比較して発現頻度に明らかな差がないことから、いずれも被験物質投与との関連性はないと判断した.

2) 死亡例

投与期間中に、0.1 mg/kg 群の雄 2 例と 2.5 mg/kg 群の雄 1 例が死亡した. また、12.5 mg/kg 群の雌 1 例を試験途中で解剖した.

上記の死亡例のうち、0.1 mg/kg 群の雄 1 例 (No. 232) では、投与 114 日から活動性低下と赤色尿、投与 146 日から下腹部汚染が散見され、投与 151 日から腫瘤 (右腹部)、投与 206 日から呼吸緩徐、投与 230 日に消瘦を呈したのち、投与 231 日に死亡した. 同群の別の 1 例 (No. 238) では、投与 322 日から腫脹 (右前肢)、投与 350 日から活動性低下、皮膚蒼白および眼球蒼白が認められ、投与 357 日に呼吸緩徐、体温低下および腹臥位を呈したのち死亡した.

2.5 mg/kg 群の雄 1 例 (No. 278) では、投与 54 日に死亡するまで、異常所見は何ら認められなかった.

12.5 mg/kg 群の雌 1 例 (No. 477) では、投与 341 日から活動性低下と鼻周囲汚染、投与 349 日から斜傾、投与 351 日から呼吸緩徐がみられ、投与 354 日に横臥位と呼吸困難を呈したことから、本例を瀕死状態と判断し、投与 354 日に試験途中で解剖した.

上記の死亡例および途中剖検例では、後述するように病理組織学的検査で死因となりうる被験物質投与に起因した変化が認められていないことから、自然発生性の変化によるものと判断した.

2. 体重測定

測定結果を Figure 1, 2, Table 3 および Appendix 3, 4 に示した.

2.5 mg/kg 群の雄で、対照群と比較して、投与 36 日以降に体重の低値が認められた.

死亡例では、0.1 mg/kg 群の雄 1 例 (No. 238) で 58.4 g/28 day の体重減少、12.5 mg/kg 群の雌 1 例 (No. 477) で投与 344 日に 83.8 g/28 day の体重減少が、いずれも投与 344 日に認められた。

3. 摂餌量の測定

測定結果を Figure 3, 4, Table 4 および Appendix 5, 6 に示した。

2.5 mg/kg 群の雄で、対照群と比較して、投与 120 日以降に摂餌量の高値が認められた。なお、摂餌量の高値は、12.5 mg/kg 群の雌にもみられたが、投与最終日にのみ認められた変化であることから、被験物質投与との関連性はないと判断した。

そのほか、摂餌量の低値が 0.1 mg/kg 群の雄に、摂餌量の高値が 0.5 mg/kg 群の雄に散見されたが、一過性の変化であるか、あるいは本変化の発現時期に高用量群では同様な変動を示さなかったことから、いずれも被験物質投与との関連性はないと判断した。

死亡例では、0.5 mg/kg 群の雄 1 例 (No. 238) と 2.5 mg/kg 群の雌 1 例 (No. 477) で投与 344 日に摂餌量の低値が認められた。

4. 尿検査

検査結果を Table 5, 6 および Appendix 7~10 に示した。

1) 投与 13 週

2.5 mg/kg 群の雄で、対照群と比較して、尿浸透圧および尿比重の高値が認められた。

2) 投与 52 週

投与 13 週時と同様な変化として、0.5 および 2.5 mg/kg 群の雄で、尿浸透圧の高値が認められた。これに加えて、0.5 mg/kg 群の雄で尿比重の高値がみられたが、2.5 mg/kg 群に同様な変動は認められなかった。

投与 13 週時にみられなかった変化として、12.5 mg/kg 群の雌で、尿量の高値と本変化に伴う尿浸透圧の低値が認められた。

5. 血液学的検査

検査結果を Table 7, 8 および Appendix 11~15 に示した。

1) 投与 13 週

2.5 mg/kg 群の雄で、対照群と比較して、血小板数の高値が認められた。また、0.5 および 2.5 mg/kg 群の雄でヘマトクリット値およびヘモグロビン量の低値が認められた。これに加えて、2.5 mg/kg 群の雄では、赤血球数の低値が認められた。

そのほか、12.5 mg/kg 群の雌で、ヘマトクリット値および MCV の低値と MCHC の高値が認められたが、赤血球数自体に変動はみられないこと、かつ投与 52 週時に同様な変動はみられなかったことから、被験物質投与との関連性はないと判断した。また、0.5 mg/kg 群の雄で、非染色性大型細胞数の高値が認められたが、高用量群に同様な変化はみられなかったことから、被験物質投与との関連性はないと判断した。

2) 投与 52 週

投与 13 週終了時と同様な変化として、2.5 mg/kg 群の雄で、血小板数の高値が認められた。これに加えて、12.5 mg/kg 群の雌でも血小板数の高値が認められた。また、0.5 および 2.5 mg/kg 群の雄で赤血球数およびヘマトクリット値の低値ないし低値傾向が認められた。

投与 13 週時にみられなかった変化として、PT および APTT の延長ないし延長傾向が 2.5 mg/kg 群の雄に認められた。

6. 血液生化学的検査

検査結果を Table 9, 10 および Appendix 16~20 に示した。

1) 投与 13 週終了時

0.5 および 2.5 mg/kg 群の雄と 12.5 mg/kg 群の雌で、対照群と比較して、A/G 比、アルブミン百分比および ALP の高値ないし高値傾向と α_2 -および β -グロブリンの低値がみられ、0.5 および 2.5 mg/kg 群の雄で、グルコースおよび BUN の高値と α_1 -グロブリンの低値が認められた。また、12.5 mg/kg 群の雌では、総蛋白質の高値も認められた。

そのほか、0.5 および 2.5 mg/kg 群の雄でナトリウムの低値とカリウムの高値、2.5 mg/kg 群の雄で無機リンの高値が認められたが、同様な変動は投与 52 週時に認められなかったことから、被験物質投与との関連性はないと判断した。また、0.5 および 12.5 mg/kg 群の雌で、総ビリルビンの低値がみられたが、極めて軽微な減少性の変動であったことから、被験物質投与との関連性はないと判断した。

2) 投与 52 週終了時

投与 13 週終了時と同様な変化として、0.5 および 2.5 mg/kg 群の雄と 12.5 mg/kg 群の雌で、対照群と比較して、A/G 比および ALP の高値ないし高値傾向と α_1 -および α_2 -グロブリンの低値ないし低値傾向がみられ、0.5 および 2.5 mg/kg 群の雄で、アルブミン百分比の高値が認められた。また、2.5 mg/kg 群の雄では、BUN の高値と β -グロブリンの低値がみられ、12.5 mg/kg 群の雌では、グルコースの高値も認められた。

そのほか、12.5 mg/kg 群の雌で、総ビリルビンの低値がみられたが、極めて軽微な減少性の変

動であったことから、被験物質投与との関連性はないと判断した。また、0.5 mg/kg 群の雄で無機リンの高値がみられたが、高用量群に同様な変動はみられなかったことから、被験物質投与との関連性はないと判断した。

7. 剖検

検査結果を Table 11, 12 および Appendix 21~25 に示した。

1) 投与 13 週終了時

2.5 mg/kg 群の雄 5 例, 12.5 mg/kg 群の雌 1 例で肝臓の肥大が認められた。

そのほか、12.5 mg/kg 群の雌で皮膚の脱毛が認められたが、1 例のみの限局した変化であったことから、被験物質投与との関連性はないと判断した。また、0.5 mg/kg 群の雌 1 例で腎盂拡張が認められたが、高用量群に同様な変化みられていないことから、被験物質投与との関連性はないと判断した。また、対照群のみの変化として、雄 1 例で腎臓の小陥凹、雌 1 例で胸腺の暗赤色化、ほかの雌 1 例で腎臓の灰白色腫瘍が認められた。

2) 投与 52 週終了時

投与 13 週終了時と同様な変化として、2.5 mg/kg 群の雄 9 例, 12.5 mg/kg 群の雌 5 例で肝臓の肥大が認められた。更に、肝臓の肥大は 0.5 mg/kg 群の雄 7 例にも認められた。

投与 13 週終了時にみられなかった変化として、2.5 mg/kg 群の雄 2 例と 12.5 mg/kg 群の雌 1 例で肝臓の灰白色斑が認められた。

そのほか、肺の暗赤色化、精巣および精巣上体の小型化、前立腺の暗赤色点、2.5 mg/kg 群の雄にみられ、肝臓の暗赤色斑が 2.5 mg/kg 群の雌 1 例と 2.5 mg/kg 群の雄 1 例に、下垂体の灰白色結節が 2.5 および 12.5 mg/kg 群の雌に、卵巣囊の拡張および子宮の内膜ポリープが 12.5 mg/kg 群の雌にみられたが、これらの変化はいずれも 1 例のみの軽度な変化であったことから、被験物質投与との関連性はないと判断した。また、対照群を含む各投与群の雄ないし雌で胼胝（後肢）が散見され、胼胝に伴う後肢の腫脹あるいは膝窩リンパ節の肥大を示す例も認められた。さらに、胸腺の小型化が対照群を含む各投与群の雌雄に、肺の白色点に対照群の雌雄と 2.5 mg/kg 群の雄に、脾臓の灰白色斑が対照および 0.1 mg/kg 群の雄に、心臓の灰白色化が対照、0.5 および 2.5 mg/kg 群の雄に、肝臓の横隔膜ヘルニアが対照および 12.5 mg/kg 群の雌に、卵巣の嚢胞、乳腺の乳汁貯留、下垂体の肥大または暗赤色点、副腎の褐色点、皮下の灰白色腫瘍または白色結節が対照群を含む各投与群の雌に、甲状腺の片側性の欠損と対側の肥大が 0.1 mg/kg 群の雄に、腎臓の小陥凹と皮膚の白色結節が 0.5 mg/kg 群の雄に、卵巣の肥大と副腎の肥大が 2.5 mg/kg 群の雌にそれぞれ認められた。これらの変化については、高用量群（雄で 2.5 mg/kg, 雌で 12.5 mg/kg）に同様な

変化がみられないか、あるいは対照群と比較してその発生頻度に明らかな差が認められなかったことから、いずれも被験物質投与との関連性はないと判断した。また、対照群のみの変化として、雄2例に肝臓の褪色が認められた。

3) 死亡例

0.5 mg/kg 群の雄1例 (No. 232) では、腎臓の灰白色腫瘍および表面の粗造化、膀胱の赤色尿の貯留、脾臓の肥大、精巣および胸腺の小型化並びに副腎の肥大が認められた。同群の残りの雄1例 (No. 238) では、前肢の淡赤色腫瘍、肝臓の褪色、腎臓表面の粗造化並びに胸腺の小型化が認められた。

2.5 mg/kg 群の雄1例 (No. 278) では、肺の暗赤色斑および胸腺の暗赤色点が認められた。

12.5 mg/kg 群の雌1例 (No. 477) では、下垂体の淡赤色腫瘍が認められ、食道壁の肥厚、前胃の穿孔および粘膜肥厚、更に穿孔部を覆うように脂肪組織が癒着していた。また、同例では乳腺の乳汁貯留並びに胸腺の小型化も認められた。

8. 器官重量の測定

測定結果を Table 13, 14 および Appendix 26~31 に示した。

1) 投与 13 週終了時

0.5 および 2.5 mg/kg 群の雄と 12.5 mg/kg 群の雌で、肝臓の絶対および相対重量の高値が認められた。また、28 日間反復投与毒性試験¹⁾と同様な変化として、2.5 mg/kg 群の雄で腎臓の相対重量の高値が認められた。

そのほか、2.5 mg/kg 群の雄で、副腎の絶対重量の低値と脳、心臓および精巣の相対重量の高値が認められたが、絶対あるいは相対重量のいずれかの変動であることから、最終体重の低値に起因した二次的変化であり、被験物質投与との関連性はないと判断した。また、甲状腺の絶対重量の高値が 0.1 mg/kg 群の雄に、精巣上体の絶対および相対重量の低値が 0.5 mg/kg 群の雄に、下垂体および甲状腺の相対重量の高値が 2.5 mg/kg 群の雌に、脾臓の絶対および相対重量の低値が 0.5 mg/kg 群の雌に認められたが、高用量群 (雄で 2.5 mg/kg, 雌で 12.5 mg/kg) に同様な変動はみられなかったことから、被験物質投与との関連性はないと判断した。

2) 投与 52 週終了時

投与 13 週終了時と同様な変化として、0.5 および 2.5 mg/kg 群の雄と 12.5 mg/kg 群の雌で、肝臓の絶対および相対重量の高値が認められた。また、28 日間反復投与毒性試験¹⁾と同様な変化として、2.5 mg/kg 群の雄で腎臓の相対重量の高値が認められた。

そのほか、2.5 mg/kg 群の雄で脳、下垂体、甲状腺、心臓、肺、精巣上体および精巣重量の高

値がみられたが、相対重量のみの変動であることから、最終体重の低値に起因した二次的変化であり、被験物質投与との関連性はないと判断した。

9. 病理組織学的検査

検査結果を Table 15, 16 および Appendix 32~36 に示した。

1) 投与 13 週終了時

肝臓では、小葉中心部の軽度ないし中等度な肝細胞肥大が、雄では 0.5 mg/kg 群の 3 例と 2.5 mg/kg 群の 9 例に、雌では 12.5 mg/kg 群の 6 例にみられ、肥大した肝細胞の細胞質は好酸性顆粒状を呈していた。

そのほか、腎臓の好塩基性尿細管と腎盂の好中球浸潤が、2.5 mg/kg 群の雄に認められたが、1 例のみの軽度な変化であったことから、被験物質投与との関連性はないと判断した。また、対照および高用量群 (雄で 2.5 mg/kg, 雌で 12.5 mg/kg) の雄ないし雌では、食道筋層の線維化、甲状腺の鰹後体遺残、肺胞内の泡沫細胞集積、肺動脈の鉍質沈着、心臓および前立腺の単核細胞浸潤、副腎の巣状の皮質細胞肥大が散見された。更に、肝臓では、小葉中間帯の肝細胞の脂肪変性が 0.1 mg/kg 群の雄に、肝細胞の巣状壊死が対照, 0.5 および 2.5 mg/kg 群の雄と 2.5 mg/kg 群の雌に、肝臓の単核細胞浸潤が対照, 0.1 および 0.5 mg/kg 群の雄と対照, 2.5 および 12.5 mg/kg 群の雌に認められた。これらの変化については、高用量群 (雄で 2.5 mg/kg, 雌で 12.5 mg/kg) に同様な変化がみられないか、あるいは対照群と比較してその程度および発生頻度に明らかな差が認められなかったことから、いずれも被験物質投与との関連性はないと判断した。また、対照群では、雄で腎臓の蛋白円柱、大脳側脳室の拡張、雌で小葉辺縁部の肝細胞の脂肪変性、脾臓の巣状の腺房萎縮、胸腺の出血、腎臓の皮髄境界部の鉍質沈着と腎芽腫が認められた。

2) 投与 52 週終了時

投与 13 週終了時と同様な変化として、肝臓において小葉中心部の軽度ないし中等度な肝細胞肥大が、雄では 0.5 mg/kg 群の 5 例と 2.5 mg/kg 群の 8 例に、雌では 12.5 mg/kg 群の 4 例に認められ、肥大した肝細胞の細胞質は好酸性顆粒状を呈していた。

投与 13 週終了時にみられなかった変化として、肝臓では、肝細胞への軽度なりポフスチン沈着 (シユモール反応：陽性、ベルリン青染色およびホール法：陰性) が 2.5 mg/kg 群の雄 6 例と 12.5 mg/kg 群の雌 2 例に、軽度ないし中等度な明細胞性変異肝細胞巣が 0.1 mg/kg 群の雄 1 例と 0.5 および 2.5 mg/kg 群の雄各 7 例に、軽度な嚢胞状変性が 0.1 および 0.5 mg/kg 群の雄各 2 例と 2.5 mg/kg 群の雄 4 例に認められた。また、2.5 mg/kg 群の雄では、肝細胞の軽度な巣状壊死の発生頻度が、対照群と比較してやや増加する傾向が認められた (発生頻度：4/10 例)。

そのほか、2.5 mg/kg 群の雄では、誤嚥性肺炎、前立腺の出血、下垂体前葉の嚢胞、甲状腺間質への好酸性物質沈着、精巣のライディッヒ細胞の巣状過形成と精細管の萎縮および精巣上体の精子減少がみられ、12.5 mg/kg 群の雌では、腺胃粘膜の好中球浸潤、盲腸筋層の線維化、卵巢嚢の拡張、子宮の内膜間質ポリープ、甲状腺の C 細胞過形成、腎臓の尿細管上皮および腎盂移行上皮の過形成、耳下腺、膵臓並びにハーダー腺のリンパ球浸潤と気管粘膜固有層の好中球浸潤並びに大腿骨および胸骨骨髓の巣状萎縮が認められた。これらの変化については、低頻度かつ軽度な変化であったことから、被験物質投与との関連性はないと判断した。

また、対照群および高用量群の雌雄ほぼ全例で胸腺の萎縮がみられ、対照群および高用量群を通して、肺胞内の泡沫細胞集積、肺動脈の鉍質沈着、心臓の単核細胞浸潤および心筋層の線維化、膵臓の巣状の腺房萎縮、腎臓の好塩基性尿細管および蛋白円柱、腎臓の皮質、腎盂あるいは腎盂腔への細胞（単核細胞ないし好中球）浸潤、腎乳頭部あるいは腎盂の鉍質沈着、甲状腺の鰓後体遺残、下垂体前葉の過形成、副腎の巣状の皮質細胞肥大と過形成が散見された。また、対照群および高用量群の雄では腺胃の腺腔拡張、膵臓の巣状の腺房細胞過形成、前立腺の萎縮と単核細胞浸潤が、雌では脾臓の赤脾髄の褐色色素沈着、卵巢の嚢胞、子宮腺上皮細胞の扁平上皮化生、腔粘膜の粘液変性、乳腺の小葉過形成、腺房／導管の拡張、副腎の血管拡張が散見されたほか、肉眼的な皮下の灰白色腫瘍または白色結節に対応して、乳腺の線維腺腫、乳腺腫および乳腺癌が認められた。更に、肝臓では、単核細胞浸潤が対照、0.1 および 2.5 mg/kg 群の雄と 12.5 mg/kg 群の雌に、小葉辺縁部の肝細胞の脂肪変性が対照群の雌雄と 0.1 mg/kg 群の雄に、血管拡張が 2.5 mg/kg 群の雄に、肝細胞腺腫が 12.5 mg/kg 群の雌に、好塩基性変異肝細胞巣が対照、2.5 および 12.5 mg/kg 群の雌に認められた。これらの変化については、高用量群（雄で 2.5 mg/kg、雌で 12.5 mg/kg）に同様な変化がみられないか、あるいは対照群と比較してその程度および発生頻度に明らかな差が認められないことから、いずれも被験物質投与との関連性はないと判断した。また、剖検時に胼胝（後肢）がみられた例では、当該部に潰瘍がみられ、潰瘍に関連して肝臓および脾臓の髓外造血、大腿骨骨髓の造血亢進並びに膝窩リンパ節の形質細胞の増加を伴う例もみられた。対照群のみの変化として、雄で膵臓のラ氏島の線維化、脾臓の被膜肥厚、腎盂の出血、膀胱筋層の好中球浸潤と精巣上体の単核細胞浸潤が認められた。

3) 死亡例

2.5 mg/kg 群の雄 1 例 (No. 278) では、肝臓の小葉中心部の軽度な肝細胞肥大、肺の軽度な出血と浮腫、胸腺の軽度な出血および下垂体後葉の軽度な嚢胞が認められたが、死因を特定するに至らなかった。

12.5 mg/kg 群の雌 1 例 (No. 477) では、下垂体前葉の腺腫が認められ、本所見が死因と判断し

た。また、同例では食道の軽度な潰瘍、前胃の軽度な穿孔性潰瘍、胸腺の中等度な萎縮、脾臓の白脾髄の軽度な萎縮および赤脾髄の軽度な褐色色素沈着、卵巣の軽度な萎縮、腔内腔への軽度な好中球滲出、乳腺の腺房／導管の中等度な拡張が認められた。

0.1 mg/kg 群の雄 1 例 (No. 232) では、腎芽腫が認められ、本所見が死因と判断した。また、同例では胸腺の重度な萎縮、腸間膜リンパ節の軽度な萎縮、脾臓の軽度な白脾髄の萎縮と髓外造血、大腿骨および胸骨骨髓の軽度な造血亢進、副腎束状帯の軽度なびまん性皮質細胞肥大、大動脈の中膜および腎臓皮質の中等度な鉍質沈着、肺胞内の軽度な泡沫細胞集積、精巣の軽度な精細管萎縮、軽度な前立腺炎、甲状腺の軽度な鰓後体遺残が認められた。

0.1 mg/kg 群の残りの雄 1 例 (No. 238) では、前肢に横紋筋肉腫が認められ、本所見が死因と判断した。また、同例では肝臓の小葉中心部の軽度な肝細胞空胞化と壊死、胸腺の中等度な萎縮、脾臓の軽度な髓外造血、大腿骨および胸骨骨髓の軽度な造血亢進、腺胃の軽度なびらん、腎臓の中等度な好塩基性尿細管、心臓の軽度な単核細胞浸潤が認められた。

考 察

2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールをラットに雄は0(対照群), 0.1, 0.5 および 2.5 mg/kg, 雌は0(対照群), 0.5, 2.5 およ 12.5 mg/kg の用量で13 または 52 週間反復経口投与した。

投与期間を通して、被験物質投与に起因した死亡の発生および一般状態の異常所見は認められなかった。

肝臓では、投与13 および 52 週終了時に、0.5 および 2.5 mg/kg 群の雄と 12.5 mg/kg 群の雌で重量の高値がみられ、2.5 mg/kg 群の雄と 12.5 mg/kg 群の雌で肥大、0.5 および 2.5 mg/kg 群の雄と 12.5 mg/kg 群の雌で小葉中心部の肝細胞肥大が認められた。また、52 週間投与終了時に、2.5 mg/kg 群の雄と 12.5 mg/kg 群の雌で灰白色斑がみられ、2.5 mg/kg 群の雄と 12.5 mg/kg 群の雌で肝細胞へのリポフスチン沈着、0.1, 0.5 および 2.5 mg/kg 群の雄で明細胞性変異肝細胞巣と嚢胞状変性の発現例数の増加が認められた。更に、肝機能に関連すると思われる変化として、投与13 ないし 52 週終了時に、0.5 および 2.5 mg/kg 群の雄と 12.5 mg/kg 群の雌で、血清の A/G 比、アルブミン百分比、ALP あるいはグルコースの高値ないし高値傾向と α_1 、 α_2 あるいは β -グロブリンの低値がみられ、12.5 mg/kg 群の雌では総蛋白質の高値も認められた。また、2.5 mg/kg 群の雄では、凝固系検査で PT および APTT の延長ないし延長傾向も認められた。上述の肝細胞肥大については、薬物代謝酵素の誘導による滑面小胞体の増加やペルオキシゾームの増加などで生じることが知られている³⁾。本試験でみられた肝細胞肥大は、小葉中心部にみられていること、かつ肥大した肝細胞の細胞質が好酸性顆粒状を呈していたことから、ペルオキシゾームの増加の可能性が考えられた。また、肝細胞へのリポフスチン沈着、変異肝細胞巣および嚢胞状変性については、健常動物においても加齢性変化として低頻度ながら観察されるが、本試験では対照群に同様の変化がないか、あるいは高用量群でその発現例数が有意に増加したことから、被験物質投与との関連性が考えられた。しかし、ペルオキシゾーム誘導剤(クロフィブレートに代表される抗脂血症剤やフタル酸エステルなどの可塑剤)の長期投与によって肝細胞のリポフスチンの増加がみられ、更に、げっ歯類では肝細胞腫瘍の発生頻度が増加することが知られている^{3,4)}。本試験においても、被験物質投与による肝細胞のペルオキシゾーム増加の可能性が13 週間の投与時点から示唆されていること、また、リポフスチン沈着、変異肝細胞巣および嚢胞状変性は13 週間の投与ではみられず、52 週間の長期投与で発現したことから、これらの変化はペルオキシゾームの増加に伴って二次的に生じた可能性が推察された。なお、げっ歯類における肝発がんを誘発するペルオキシゾーム誘導剤に関しては、直接 DNA に対して傷害を与えない非遺伝毒性(非変異原性)発がん物質と考えられており、これらの長期投与で生じる肝発がんはげっ歯類特有の変化であること

が示唆されている^{5,6,7)}。上述した変化に加えて、高用量群の雄では、肝細胞巣状壊死の発現例数の増加傾向がみられ、被験物質投与との関連性が疑われたが、肝細胞肥大(ペルオキシゾームの増加が窺われる変化)との関連については明らかでなかった。

上述のほか、体重、摂餌量、血液学的検査、血液生化学的検査および器官重量において、28日間反復投与毒性試験¹⁾と同様な変化が認められた。すなわち、体重の低値が、2.5 mg/kg 群の雄で投与36日以降に、摂餌量の高値が、2.5 mg/kg 群の雄で投与120日以降に認められた。また、血小板数の高値が、2.5 mg/kg 群の雄と12.5 mg/kg 群の雌で投与13あるいは52週終了時に、赤血球数、ヘマトクリット値あるいはヘモグロビン量の低値が、0.5 および2.5 mg/kg 群の雄で投与13 および52週終了時にみられ、BUNの高値が、0.5 および2.5 mg/kg 群の雄で投与13あるいは52週終了時に認められた。更に、腎臓重量(相対重量)の増加が、2.5 mg/kg 群の雄で投与13 および52週終了時に認められた。そのほか、本試験では、上述のBUNの高値や腎臓重量の高値との関連性が考えられる変化として、0.5 および2.5 mg/kg 群の雄で尿浸透圧あるいは尿比重の高値が投与13 および52週時に認められた。これらの尿パラメータの変動については、28日間反復投与毒性試験において同様な変化は認められていないことから¹⁾、長期投与による影響を示唆するものと考えられた。なお、12.5 mg/kg 群の雌では、尿量の高値と本変化に伴う尿浸透圧の低値が投与52週時にみられたが、血液生化学的検査および病理組織学的検査において、本変化に関連する異常所見は何ら認められなかったことから、毒性学的意義に乏しい変化と捉えている。

以上のことから、本試験条件下における2-(2'-ヒドロキシ-3',5'-ジ-tert-ブチルフェニル)ベンゾトリアゾールの52週間反復投与における無影響量(NOEL)は、雄では肝臓への病理組織学的影響と血清の蛋白、グルコースおよびALPの変動、尿パラメータの変動とBUNの変動、並びに赤血球系パラメータの変動がみられなかった0.1 mg/kg/dayであり、雌では肝臓への病理組織学的影響と血清の蛋白、グルコースおよびALPの変動、並びに血小板数の変動がみられなかった2.5 mg/kg/dayと判断した。

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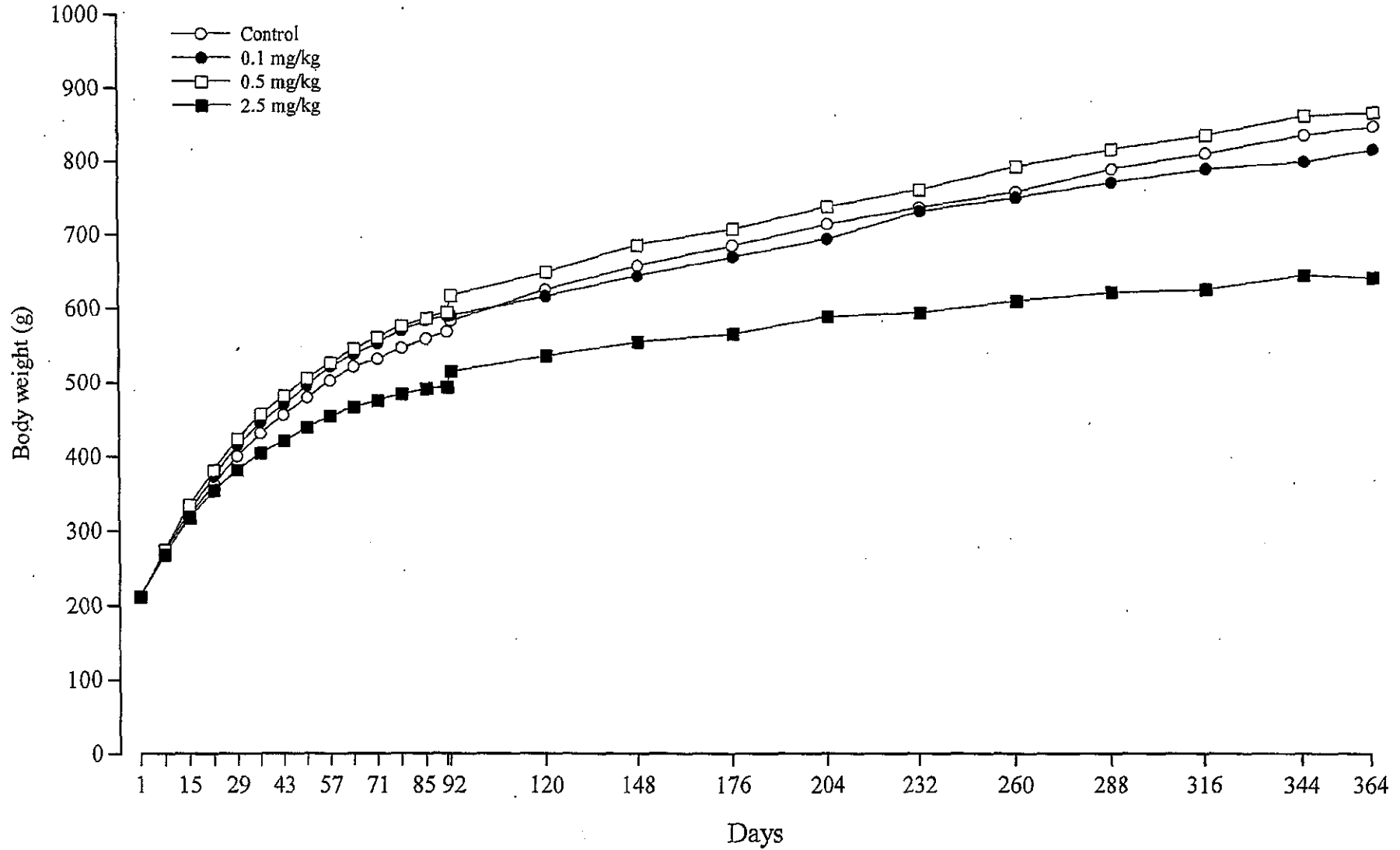


Figure 1 Body weight changes (Male)

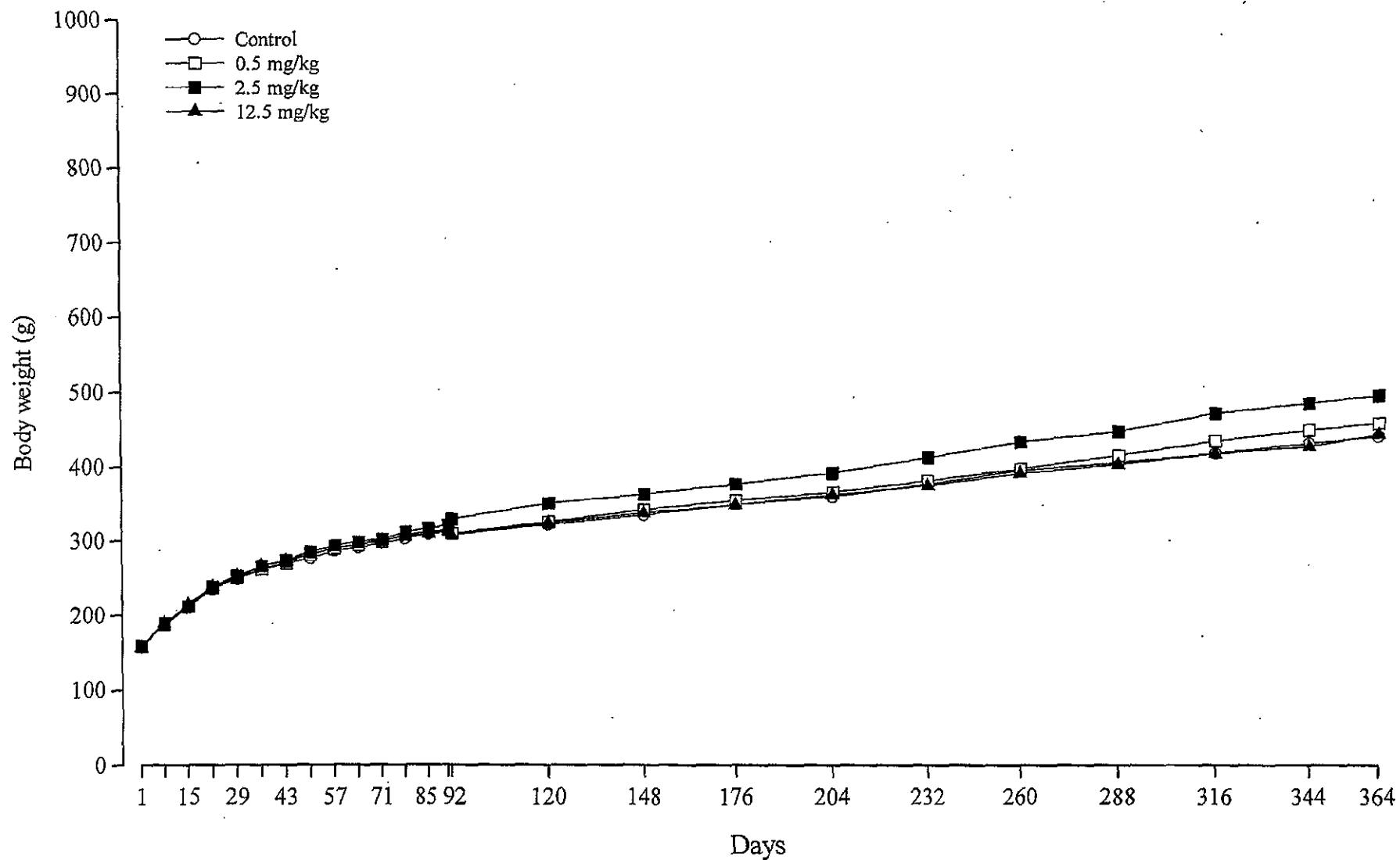


Figure 2 Body weight changes (Female)

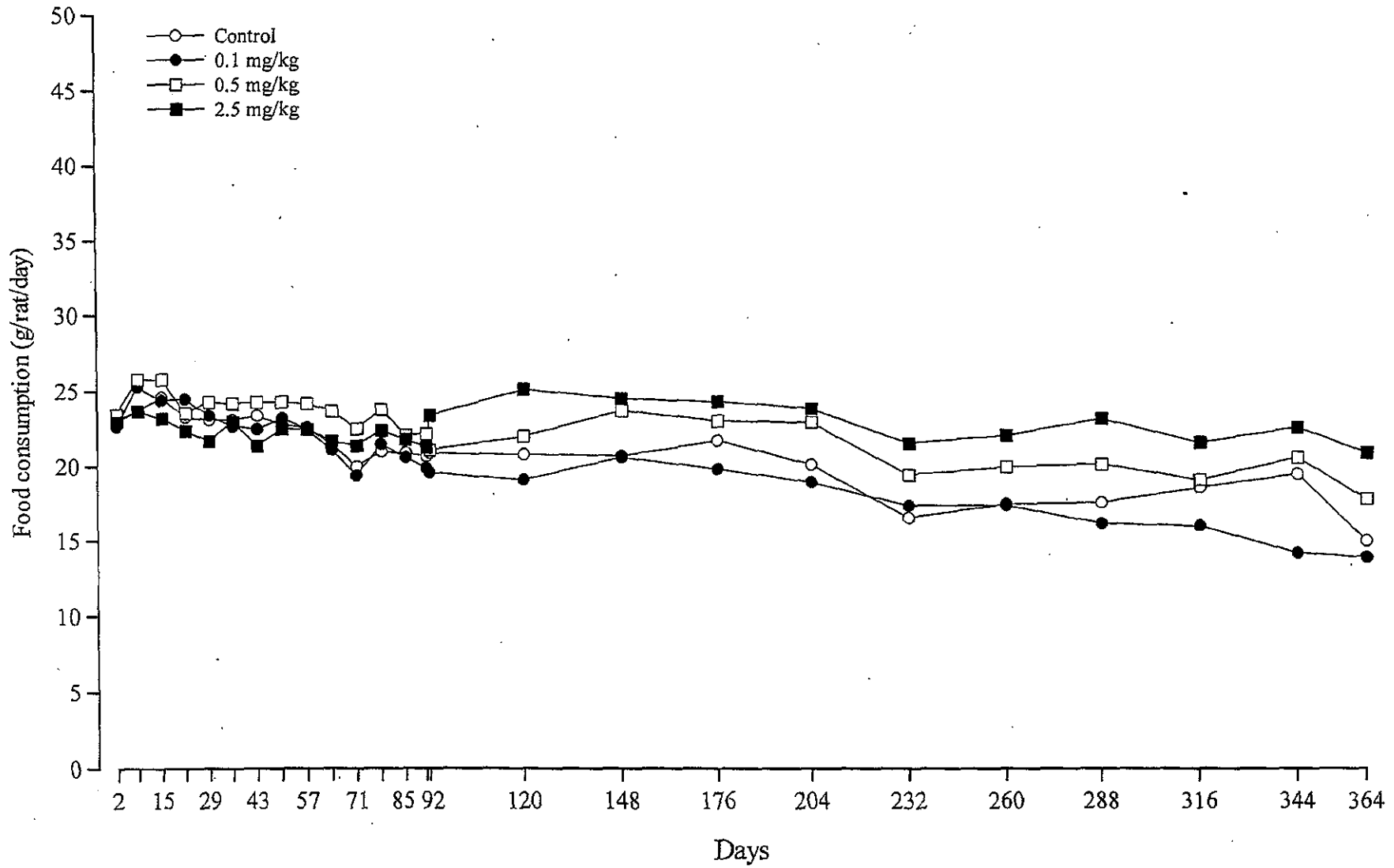


Figure 3 Food consumption (Male)
64

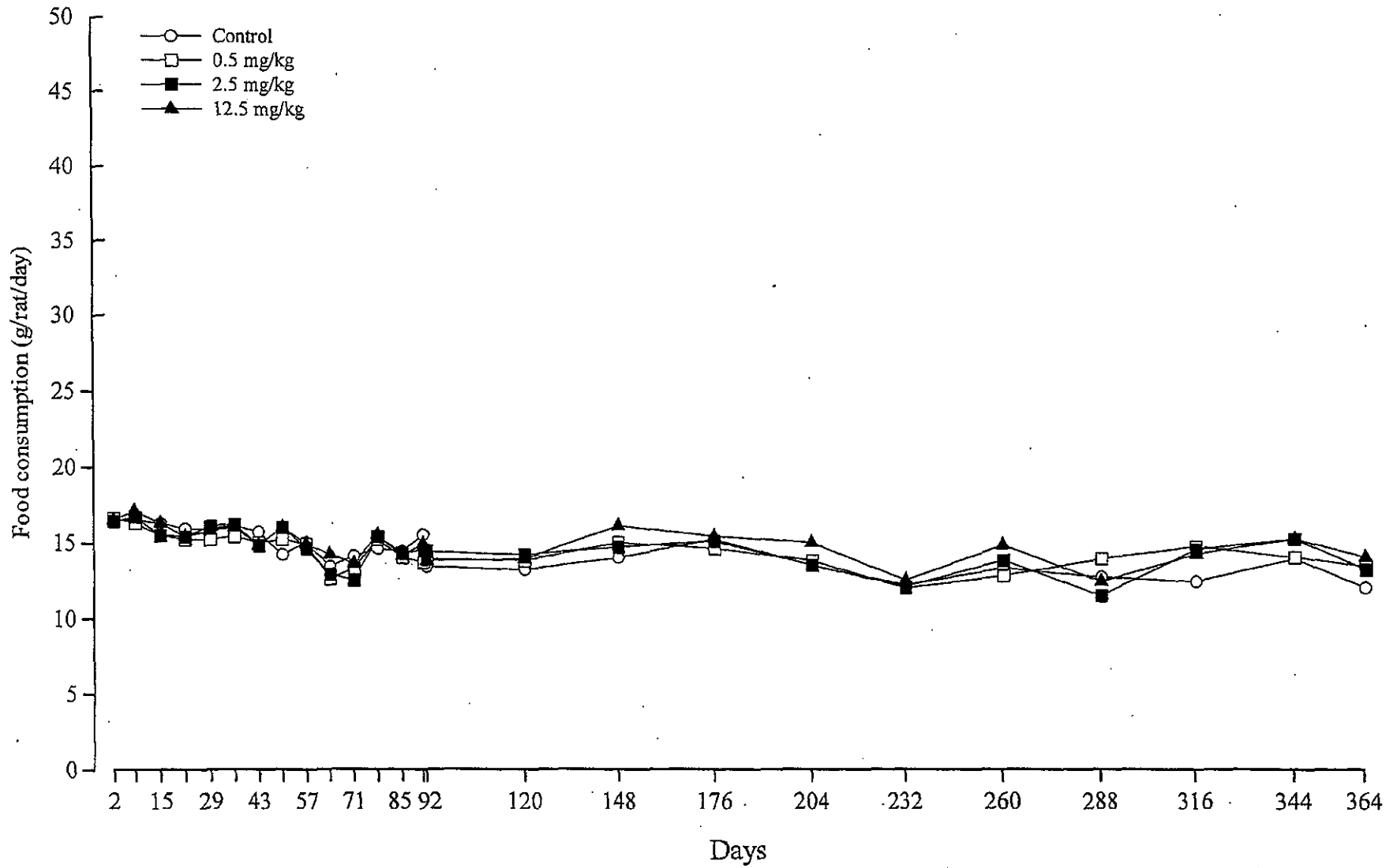


Figure 4 Food consumption (Female)

Table 1 Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------|----------------------|----------------------|------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | |
| Male | Control | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.1 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Reddish urine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled lower abdomen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Emaciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pale skin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Pale eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Prone position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Hypothermia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 0.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 2.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 1 - continued Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------------|--------------------|----------------------|--------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| | | | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 |
| Male | Control | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.1 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Reddish urine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled lower abdomen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Emaciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Pale skin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Pale eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Prone position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Hypothermia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 0.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| No abnormality | 20 | | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| Corn | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Abnormality of tooth | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 2.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 1 - continued
Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------|----------------------|----------------------|------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| | | | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 | 61 | 62 | 63 | 64 | 65 |
| Male | Control | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.1 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Reddish urine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled lower abdomen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Emaciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Pale skin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Pale eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Prone position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Hypothermia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 0.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| No abnormality | | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| Corn | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 2.5 mg/kg | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | |
| | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 1 - continued
Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------|----------------------|----------------------|------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| | | | 66 | 67 | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 | 84 | 85 | 86 | 87 |
| Male | Control | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.1 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Reddish urine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled lower abdomen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Emaciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pale skin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Pale eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Prone position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Hypothermia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 0.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 2.5 mg/kg | Number of examined | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | |
| | No abnormality | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 1 - continued Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------|----------------------|----------------------|------|----|----|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 88 | 89 | 90 | 91 | 92 | 93 | 94 | 95 | 96 | 97 | 98 | 99 | 100 | 101 | 102 | 103 | 104 | 105 | 106 | 107 | 108 | 109 |
| Male | Control | Number of examined | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.1 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Reddish urine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled lower abdomen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Emaciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pale skin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Pale eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Prone position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Hypothermia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 0.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 20 | 20 | 20 | 20 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 10 | 10 | 10 | 10 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Abnormality of tooth | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | |
| 2.5 mg/kg | Number of examined | 19 | 19 | 19 | 19 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 19 | 19 | 19 | 19 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 1 - continued Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------------|--------------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 110 | 111 | 112 | 113 | 114 | 115 | 116 | 117 | 118 | 119 | 120 | 121 | 122 | 123 | 124 | 125 | 126 | 127 | 128 | 129 | 130 | 131 |
| Male | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.1 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 9 | 9 | 9 | 9 | 10 | 9 | 9 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Reddish urine | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled lower abdomen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Emaciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Pale skin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Pale eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Prone position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Hypothermia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Corn | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Abnormality of tooth | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 1 - continued Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------------|--------------------|----------------------|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 132 | 133 | 134 | 135 | 136 | 137 | 138 | 139 | 140 | 141 | 142 | 143 | 144 | 145 | 146 | 147 | 148 | 149 | 150 | 151 | 152 | 153 |
| Male | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.1 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 9 | 9 | 9 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 9 | 9 | 9 | 10 | 10 | 10 | 9 | 9 | 9 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Reddish urine | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled lower abdomen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Emaciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Pale skin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Pale eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Prone position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Hypothermia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| No abnormality | 10 | | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 9 | |
| Corn | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Abnormality of tooth | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | |
| 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 1 - continued Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------|----------------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 154 | 155 | 156 | 157 | 158 | 159 | 160 | 161 | 162 | 163 | 164 | 165 | 166 | 167 | 168 | 169 | 170 | 171 | 172 | 173 | 174 | 175 |
| Male | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.1 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Reddish urine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 |
| | | Soiled lower abdomen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Emaciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pale skin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Pale eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Prone position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Hypothermia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 9 | 9 | 9 | 9 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Abnormality of tooth | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 1 - continued
Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | | | |
|----------------|----------------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|---|
| | | | 176 | 177 | 178 | 179 | 180 | 181 | 182 | 183 | 184 | 185 | 186 | 187 | 188 | 189 | 190 | 191 | 192 | 193 | 194 | 195 | 196 | 197 | | |
| Male | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | | |
| | | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | | |
| | | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 0.1 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | | Reddish urine | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | | Soiled lower abdomen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Emaciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pale skin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Pale eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Prone position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Hypothermia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | | |
| | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | | |
| | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | | |
| | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |

Table 1 - continued Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | | |
|----------------|----------------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---|
| | | | 198 | 199 | 200 | 201 | 202 | 203 | 204 | 205 | 206 | 207 | 208 | 209 | 210 | 211 | 212 | 213 | 214 | 215 | 216 | 217 | 218 | 219 | |
| Male | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | |
| | | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.1 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | | Reddish urine | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled lower abdomen | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | | Mass | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | | Emaciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pale skin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Pale eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Prone position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Hypothermia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | | |
| | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | |
| | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | | |
| | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | | |
| | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |

Table 1 - continued Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------|----------------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 220 | 221 | 222 | 223 | 224 | 225 | 226 | 227 | 228 | 229 | 230 | 231 | 232 | 233 | 234 | 235 | 236 | 237 | 238 | 239 | 240 | 241 |
| Male | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.1 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | No abnormality | 9 | 9 | 9 | 9 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | | Corn | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | | Hypoactivity | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Reddish urine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled lower abdomen | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Bradypnea | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Emaciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pale skin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Pale eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Prone position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Hypothermia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
| | Corn | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | |
| | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | |
| | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 1 - continued Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | |
|-------------------|----------------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 242 | 243 | 244 | 245 | 246 | 247 | 248 | 249 | 250 | 251 | 252 | 253 | 254 | 255 | 256 | 257 | 258 | 259 | 260 | 261 | 262 |
| Male | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| | | Corn | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 |
| | 0.1 mg/kg | Number of examined | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | No abnormality | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Reddish urine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled lower abdomen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Swelling of limbs | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Bradypnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Emaciation | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Pale skin | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Pale eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Prone position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Hypothermia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
| | Corn | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | |
| | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | |
| | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 1 - continued Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------|----------------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 264 | 265 | 266 | 267 | 268 | 269 | 270 | 271 | 272 | 273 | 274 | 275 | 276 | 277 | 278 | 279 | 280 | 281 | 282 | 283 | 284 | 285 |
| Male | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| | | Corn | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| | | Swelling of limbs | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.1 mg/kg | Number of examined | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | No abnormality | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Reddish urine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled lower abdomen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Emaciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pale skin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Pale eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Prone position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Hypothermia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | |
| | Corn | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | |
| | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 1 - continued Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------|----------------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 286 | 287 | 288 | 289 | 290 | 291 | 292 | 293 | 294 | 295 | 296 | 297 | 298 | 299 | 300 | 301 | 302 | 303 | 304 | 305 | 306 | 307 |
| Male | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 7 | 7 | 7 | 7 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| | | Corn | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.1 mg/kg | Number of examined | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | No abnormality | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Reddish urine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled lower abdomen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Emaciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pale skin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Pale eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Prone position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Hypothermia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | |
| | Corn | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | |
| | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 1 - continued Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | | |
|----------------|----------------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---|
| | | | 308 | 309 | 310 | 311 | 312 | 313 | 314 | 315 | 316 | 317 | 318 | 319 | 320 | 321 | 322 | 323 | 324 | 325 | 326 | 327 | 328 | 329 | |
| Male | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | | No abnormality | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | |
| | | Corn | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 0.1 mg/kg | Number of examined | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | |
| | | No abnormality | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
| | | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | | Reddish urine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | | Soiled lower abdomen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | | Emaciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Pale skin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | |
| Pale eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | |
| Prone position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | |
| Hypothermia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | |
| 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | | |
| | No abnormality | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | | |
| | Corn | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | | |
| | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | | |
| | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | | |
| | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |

Table 1.- continued Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------|----------------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 330 | 331 | 332 | 333 | 334 | 335 | 336 | 337 | 338 | 339 | 340 | 341 | 342 | 343 | 344 | 345 | 346 | 347 | 348 | 349 | 350 | 351 |
| Male | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| | | Corn | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.1 mg/kg | Number of examined | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | No abnormality | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 5 | 5 | 5 | 4 | 3 | 3 |
| | | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 4 | 5 | 5 |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| | | Reddish urine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled lower abdomen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Emaciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pale skin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | | |
| Pale eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Prone position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Hypothermia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 5 | 5 | 5 | |
| | Corn | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 5 | 5 | 5 | |
| | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 8 | 8 | 8 | |
| | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 1 - continued Incidence of clinical signs
Male

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | |
|----------------|----------------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 352 | 353 | 354 | 355 | 356 | 357 | 358 | 359 | 360 | 361 | 362 | 363 | 364 |
| Male | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| | | Corn | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| | | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.1 mg/kg | Number of examined | 9 | 9 | 9 | 9 | 9 | 9 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | | No abnormality | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| | | Corn | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| | | Hypoactivity | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Reddish urine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled lower abdomen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Dead | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Swelling of limbs | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Bradypnea | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Emaciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pale skin | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Pale eyes | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Prone position | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Hypothermia | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 5 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 3 | 3 | |
| | Corn | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | |
| | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 9 | |
| | Corn | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | |
| | Dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Swelling of limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | |

Table 2 Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------------|----------------|----------------------|------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | |
| Female | Control | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Corn Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 12.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Loss of hair | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Hypoactivity | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Soiled perinaris | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Torticollis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Bradypnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Lateral position | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Dyspnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Imminently sacrifice | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |

Table 2.- continued Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------------|--------------------|----------------------|------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| | | | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 |
| Female | Control | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.5 mg/kg | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2.5 mg/kg | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 12.5 mg/kg | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Loss of hair | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Soiled perianis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Torticollis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Lateral position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Dyspnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Imminently sacrifice | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |

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Table 2 - continued
Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------------|----------------|----------------------|------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| | | | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 | 61 | 62 | 63 | 64 | 65 |
| Female | Control | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | 2.5 mg/kg | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | 12.5 mg/kg | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Loss of hair | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Hypoactivity | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Soiled perinearis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Torticollis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Bradypnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Lateral position | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Dyspnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Imminently sacrifice | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 2 - continued Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------------|--------------------|----------------------|------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| | | | 66 | 67 | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 | 84 | 85 | 86 | 87 |
| Female | Control | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 19 | 19 | 19 | 19 | 19 | 20 | 20 | 20 | 20 | 20 |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 0.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 12.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | No abnormality | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 19 | 19 | 19 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Loss of hair | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | |
| | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Soiled perinaris | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Torticollis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Lateral position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Dyspnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Imminently sacrifice | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |

Table 2 - continued
Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | |
|----------------------|--------------------|----------------------|------|----|----|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 88 | 89 | 90 | 91 | 92 | 93 | 94 | 95 | 96 | 97 | 98 | 99 | 100 | 101 | 102 | 103 | 104 | 105 | 106 | 107 | 108 |
| Female | Control | Number of examined | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 12.5 mg/kg | Number of examined | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 19 | 19 | 19 | 19 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Loss of hair | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Soiled perinearis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Torticollis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Lateral position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Dyspnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Imminently sacrifice | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |

Table 2 - continued Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | |
|----------------------|----------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 110 | 111 | 112 | 113 | 114 | 115 | 116 | 117 | 118 | 119 | 120 | 121 | 122 | 123 | 124 | 125 | 126 | 127 | 128 | 129 | 130 |
| Female | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.5 mg/kg | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | 2.5 mg/kg | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | 12.5 mg/kg | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Loss of hair | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hypoactivity | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Soiled perianis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Torticollis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Bradypnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Lateral position | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Dyspnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Imminently sacrifice | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 2 - continued Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | |
|----------------------|----------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 132 | 133 | 134 | 135 | 136 | 137 | 138 | 139 | 140 | 141 | 142 | 143 | 144 | 145 | 146 | 147 | 148 | 149 | 150 | 151 | 152 |
| Female | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 12.5 mg/kg | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Number of examined | | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| No abnormality | | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| Corn | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Mass | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Loss of hair | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Hypoactivity | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Soiled perianis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Torticollis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Bradypnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Lateral position | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Dyspnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Imminently sacrifice | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |

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Table 2 - continued Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------------|----------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 154 | 155 | 156 | 157 | 158 | 159 | 160 | 161 | 162 | 163 | 164 | 165 | 166 | 167 | 168 | 169 | 170 | 171 | 172 | 173 | 174 | 175 |
| Female | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Mass | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 12.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| No abnormality | | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| Corn | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Mass | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Loss of hair | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Hypoactivity | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Soiled perinearis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Torticollis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Bradypnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Lateral position | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Dyspnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Imminently sacrifice | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 2 - continued Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | |
|----------------------|----------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 176 | 177 | 178 | 179 | 180 | 181 | 182 | 183 | 184 | 185 | 186 | 187 | 188 | 189 | 190 | 191 | 192 | 193 | 194 | 195 | 196 |
| Female | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Mass | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 12.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| No abnormality | | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| Corn | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Mass | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Loss of hair | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Hypoactivity | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Soiled perinaris | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Torticollis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Bradypnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Lateral position | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Dyspnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Imminently sacrifice | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 2 - continued Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | |
|------------|----------------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 198 | 199 | 200 | 201 | 202 | 203 | 204 | 205 | 206 | 207 | 208 | 209 | 210 | 211 | 212 | 213 | 214 | 215 | 216 | 217 | 218 |
| Female | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Mass | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 12.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Loss of hair | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Soiled perianaris | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Torticollis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Lateral position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Dyspnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Imminently sacrifice | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 2 - continued Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------------|----------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 220 | 221 | 222 | 223 | 224 | 225 | 226 | 227 | 228 | 229 | 230 | 231 | 232 | 233 | 234 | 235 | 236 | 237 | 238 | 239 | 240 | 241 |
| Female | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Mass | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | 2.5 mg/kg | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | 12.5 mg/kg | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Loss of hair | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled perinaris | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Torticollis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Bradypnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Lateral position | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Dyspnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Imminently sacrifice | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 2 - continued Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------------|----------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 242 | 243 | 244 | 245 | 246 | 247 | 248 | 249 | 250 | 251 | 252 | 253 | 254 | 255 | 256 | 257 | 258 | 259 | 260 | 261 | 262 | 263 |
| Female | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Mass | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| | 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 12.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Loss of hair | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Hypoactivity | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Soiled perinearis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Torticollis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Bradypnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Lateral position | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Dyspnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Imminently sacrifice | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 2 - continued Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|------------|----------------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 264 | 265 | 266 | 267 | 268 | 269 | 270 | 271 | 272 | 273 | 274 | 275 | 276 | 277 | 278 | 279 | 280 | 281 | 282 | 283 | 284 | 285 |
| Female | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | | No abnormality | 8 | 8 | 8 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Corn | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Mass | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| | 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 12.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Loss of hair | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Soiled perinaris | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Torticollis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Bradypnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Lateral position | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Dyspnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Imminently sacrifice | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 2 - continued Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | | |
|----------------------|----------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| | | | 286 | 287 | 288 | 289 | 290 | 291 | 292 | 293 | 294 | 295 | 296 | 297 | 298 | 299 | 300 | 301 | 302 | 303 | 304 | 305 | 306 | 307 | |
| Female | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | | No abnormality | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Mass | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| | 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 12.5 mg/kg | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Loss of hair | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled perinarius | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Torticollis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Bradypnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Lateral position | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Dyspnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Imminently sacrifice | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 2 - continued Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | |
|----------------------|----------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 308 | 309 | 310 | 311 | 312 | 313 | 314 | 315 | 316 | 317 | 318 | 319 | 320 | 321 | 322 | 323 | 324 | 325 | 326 | 327 | 328 | 329 |
| Female | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | | No abnormality | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Mass | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| | 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 12.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Mass | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Loss of hair | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Soiled perianaris | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Torticollis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Bradypnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Lateral position | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Dyspnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Imminently sacrifice | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 2 - continued Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | | | | | | | | | | | |
|----------------------|----------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---|
| | | | 330 | 331 | 332 | 333 | 334 | 335 | 336 | 337 | 338 | 339 | 340 | 341 | 342 | 343 | 344 | 345 | 346 | 347 | 348 | 349 | 350 | 351 | |
| Female | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | | No abnormality | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Mass | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| | 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | | No abnormality | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | 2.5 mg/kg | Corn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | | Mass | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | 12.5 mg/kg | No abnormality | 10 | 10 | 10 | 10 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 8 | 8 | 8 | 8 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
| | | Corn | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| Mass | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | |
| Loss of hair | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Hypoactivity | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | |
| Soiled perinearis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | |
| Torticollis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | | |
| Bradypnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Lateral position | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Dyspnea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Imminently sacrifice | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |

Table 2 - continued
Incidence of clinical signs
Female

| Sex | Group and dose | Clinical sign | Days | | | | | | | | | | | | |
|----------------------|----------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | 352 | 353 | 354 | 355 | 356 | 357 | 358 | 359 | 360 | 361 | 362 | 363 | 364 |
| Female | Control | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| | | Abnormality of tooth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | | Mass | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| | 0.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 10 |
| | | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |
| | 2.5 mg/kg | Number of examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | No abnormality | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 7 |
| | | Corn | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 |
| | | Mass | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | 12.5 mg/kg | Number of examined | 10 | 10 | 10 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | No abnormality | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 6 | 6 | 6 | 6 | 6 | 5 |
| | | Corn | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 |
| Mass | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 3 | |
| Loss of hair | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Hypoactivity | | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Soiled perinaris | | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Torticollis | | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Bradypnea | | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Lateral position | | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Dyspnea | | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Imminently sacrifice | | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

Table 3 Body weights
Male, Female

| Sex | Group and dose | | Body weight(g) on day | | | | | | | | | | |
|--------|----------------|------|-----------------------|-------|-------|-------|-------|--------|---------|---------|---------|---------|----|
| | | | 1 | 8 | 15 | 22 | 29 | 36 | 43 | 50 | 57 | 64 | |
| Male | Control | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Mean | 212.1 | 267.5 | 320.9 | 362.2 | 400.2 | 431.3 | 456.1 | 479.2 | 501.7 | 520.9 | |
| | | S.D. | ±8.5 | ±14.3 | ±23.7 | ±30.2 | ±36.7 | ±40.0 | ±42.3 | ±44.9 | ±50.0 | ±52.9 | |
| | 0.1 mg/kg | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Mean | 212.4 | 271.5 | 327.0 | 372.7 | 414.5 | 445.6 | 469.9 | 495.1 | 521.6 | 537.6 | |
| | | S.D. | ±9.1 | ±13.6 | ±19.0 | ±24.8 | ±27.5 | ±29.6 | ±31.0 | ±33.4 | ±34.5 | ±37.3 | |
| | 0.5 mg/kg | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Mean | 211.5 | 274.5 | 334.9 | 381.2 | 423.2 | 456.6 | 481.6 | 505.5 | 526.6 | 545.0 | |
| | | S.D. | ±9.5 | ±14.6 | ±20.3 | ±25.3 | ±30.6 | ±33.6 | ±36.0 | ±38.4 | ±40.5 | ±44.1 | |
| | 2.5 mg/kg | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 19 | 19 | |
| | | Mean | 212.0 | 268.5 | 317.5 | 353.9 | 382.1 | 404.4* | 421.1** | 438.8** | 454.4** | 466.2** | |
| | | S.D. | ±10.1 | ±13.3 | ±18.7 | ±23.1 | ±25.9 | ±29.6 | ±32.2 | ±38.8 | ±42.3 | ±46.6 | |
| Female | Control | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | | Mean | 157.7 | 187.3 | 210.8 | 235.1 | 249.1 | 261.3 | 268.6 | 276.1 | 286.1 | 290.9 | |
| | | S.D. | ±8.6 | ±11.1 | ±12.6 | ±15.7 | ±16.5 | ±17.3 | ±18.1 | ±17.7 | ±21.4 | ±22.8 | |
| | 0.5 mg/kg | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | | Mean | 159.1 | 187.9 | 212.3 | 237.2 | 250.9 | 261.9 | 270.2 | 281.2 | 289.5 | 294.3 | |
| | | S.D. | ±8.3 | ±11.6 | ±13.4 | ±18.0 | ±19.3 | ±21.3 | ±21.6 | ±23.7 | ±25.5 | ±27.0 | |
| | 2.5 mg/kg | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | | Mean | 159.0 | 190.0 | 211.9 | 238.4 | 253.4 | 265.7 | 273.3 | 284.9 | 293.5 | 298.6 | |
| | | S.D. | ±7.9 | ±10.9 | ±13.1 | ±15.7 | ±17.4 | ±18.9 | ±19.8 | ±21.8 | ±23.6 | ±24.6 | |
| | 12.5 mg/kg | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | | Mean | 157.1 | 189.1 | 213.8 | 238.3 | 252.7 | 265.5 | 272.6 | 281.5 | 290.2 | 295.1 | |
| | | S.D. | ±8.4 | ±11.8 | ±13.4 | ±15.9 | ±18.3 | ±19.3 | ±18.3 | ±21.1 | ±22.5 | ±23.2 | |

*: P<0.05, **: P<0.01 (significantly different from control).

Table 3 - continued
Body weights
Male, Female

| Sex | Group and dose | | Body weight (g) on day | | | | | | | | | |
|--------|----------------|------|------------------------|---------|---------|---------|--------|--------|--------|--------|--------|---------|
| | | | 71 | 78 | 85 | 91 | 92 | 120 | 148 | 176 | 204 | 232 |
| Male | Control | N | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 531.7 | 546.4 | 558.8 | 568.3 | 583.0 | 625.2 | 657.5 | 683.9 | 713.3 | 735.3 |
| | | S.D. | ±54.6 | ±55.4 | ±59.0 | ±60.7 | ±79.8 | ±88.8 | ±102.5 | ±111.5 | ±118.1 | ±113.7 |
| | 0.1 mg/kg | N | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 9 |
| | | Mean | 553.0 | 569.9 | 583.3 | 589.4 | 590.4 | 616.0 | 643.8 | 668.9 | 693.1 | 730.0 |
| | | S.D. | ±35.9 | ±38.5 | ±40.1 | ±40.0 | ±39.5 | ±64.6 | ±69.7 | ±74.8 | ±76.4 | ±74.4 |
| | 0.5 mg/kg | N | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 560.3 | 575.9 | 586.4 | 594.3 | 617.0 | 648.9 | 685.1 | 706.5 | 736.8 | 759.3 |
| | | S.D. | ±47.1 | ±48.6 | ±49.8 | ±52.4 | ±52.7 | ±61.7 | ±71.0 | ±82.7 | ±90.7 | ±98.4 |
| | 2.5 mg/kg | N | 19 | 19 | 19 | 19 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 475.4** | 483.8** | 491.5** | 493.2** | 515.0* | 535.9* | 554.5* | 565.4* | 588.7* | 593.7** |
| | | S.D. | ±46.4 | ±49.4 | ±50.8 | ±51.8 | ±61.0 | ±59.2 | ±65.0 | ±68.2 | ±74.8 | ±82.7 |
| Female | Control | N | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | |
| | | Mean | 296.2 | 302.5 | 309.1 | 315.2 | 308.3 | 321.7 | 334.9 | 348.6 | 359.3 | 375.7 |
| | | S.D. | ±22.5 | ±24.6 | ±25.7 | ±26.8 | ±26.9 | ±29.4 | ±35.8 | ±41.2 | ±47.1 | ±56.3 |
| | 0.5 mg/kg | N | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 299.0 | 307.4 | 312.2 | 314.0 | 309.7 | 325.2 | 341.8 | 354.4 | 365.1 | 380.6 |
| | | S.D. | ±27.1 | ±28.5 | ±29.7 | ±30.6 | ±28.5 | ±36.2 | ±36.1 | ±41.0 | ±42.4 | ±46.3 |
| | 2.5 mg/kg | N | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 301.9 | 311.4 | 316.8 | 320.4 | 328.9 | 350.7 | 362.8 | 376.5 | 391.4 | 411.8 |
| | | S.D. | ±26.0 | ±28.0 | ±30.3 | ±31.7 | ±39.3 | ±46.0 | ±49.2 | ±54.3 | ±60.6 | ±70.8 |
| | 12.5 mg/kg | N | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 300.3 | 306.0 | 309.1 | 311.9 | 307.5 | 324.0 | 337.7 | 348.3 | 361.7 | 373.7 |
| | | S.D. | ±23.6 | ±24.8 | ±27.4 | ±24.6 | ±28.0 | ±31.8 | ±31.2 | ±35.4 | ±36.1 | ±37.1 |

*: P<0.05, **: P<0.01 (significantly different from control).

Table 3:- continued
Body weights
Male, Female

| Sex | Group and dose | | Body weight(g) on day | | | | |
|--------|----------------|------|-----------------------|---------|---------|---------|---------|
| | | | 260 | 288 | 316 | 344 | 364 |
| Male | Control | N | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 756.3 | 786.6 | 807.1 | 832.0 | 843.4 |
| | | S.D. | ±117.4 | ±131.2 | ±136.9 | ±145.8 | ±152.9 |
| | 0.1 mg/kg | N | 9 | 9 | 9 | 9 | 8 |
| | | Mean | 748.2 | 768.4 | 786.2 | 795.8 | 811.9 |
| | | S.D. | ±90.8 | ±101.6 | ±114.1 | ±129.1 | ±144.5 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 790.8 | 813.2 | 832.0 | 858.3 | 862.3 |
| | | S.D. | ±112.4 | ±118.0 | ±124.8 | ±136.1 | ±139.3 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 609.5** | 620.7** | 623.8** | 643.3** | 639.4** |
| | | S.D. | ±84.2 | ±88.2 | ±85.5 | ±97.1 | ±96.7 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 394.5 | 404.6 | 417.1 | 430.5 | 440.1 |
| | | S.D. | ±66.0 | ±71.8 | ±79.9 | ±85.6 | ±87.7 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 396.2 | 414.7 | 433.8 | 448.5 | 457.9 |
| | | S.D. | ±53.5 | ±57.5 | ±63.3 | ±70.3 | ±73.4 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 432.8 | 446.8 | 471.1 | 484.6 | 495.0 |
| | | S.D. | ±77.2 | ±83.2 | ±98.0 | ±99.8 | ±105.5 |
| | 12.5 mg/kg | N | 10 | 10 | 10 | 10 | 9 |
| | | Mean | 390.3 | 402.3 | 416.8 | 426.2 | 442.4 |
| | | S.D. | ±41.4 | ±48.9 | ±54.3 | ±69.0 | ±72.2 |

** : P<0.01 (significantly different from control).

Table 4 Food consumption
Male, Female

| Sex | Group and dose | | Food consumption (g) on day | | | | | | | | | | |
|--------|----------------|------|-----------------------------|-------|------|------|------|------|------|------|------|-------|----|
| | | | 2 | 8 | 15 | 22 | 29 | 36 | 43 | 50 | 57 | 64 | |
| Male | Control | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Mean | 23.1 | 23.7 | 24.6 | 23.3 | 23.1 | 23.1 | 23.4 | 22.8 | 22.6 | 21.5 | |
| | | S.D. | ±2.1 | ±2.2 | ±2.9 | ±3.1 | ±3.1 | ±2.3 | ±2.6 | ±2.4 | ±3.2 | ±3.6 | |
| | 0.1 mg/kg | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Mean | 22.7 | 25.3 | 24.4 | 24.5 | 23.4 | 22.7 | 22.5 | 23.2 | 22.5 | 21.1 | |
| | | S.D. | ±1.8 | ±2.4 | ±2.6 | ±2.6 | ±2.4 | ±2.3 | ±2.6 | ±2.7 | ±2.1 | ±2.6 | |
| | 0.5 mg/kg | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | Mean | 23.5 | 25.8* | 25.8 | 23.6 | 24.3 | 24.2 | 24.3 | 24.3 | 24.2 | 23.7* | |
| | | S.D. | ±1.9 | ±2.1 | ±2.8 | ±2.5 | ±2.1 | ±1.8 | ±1.9 | ±2.4 | ±2.2 | ±2.2 | |
| | 2.5 mg/kg | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 19 | 19 | |
| | | Mean | 23.0 | 23.7 | 23.2 | 22.4 | 21.7 | 23.0 | 21.4 | 22.5 | 22.5 | 21.7 | |
| | | S.D. | ±2.3 | ±2.1 | ±3.1 | ±2.9 | ±2.8 | ±3.1 | ±3.6 | ±3.8 | ±3.7 | ±3.0 | |
| Female | Control | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | | Mean | 16.5 | 16.5 | 16.3 | 15.9 | 15.9 | 16.1 | 15.7 | 14.2 | 15.0 | 13.4 | |
| | | S.D. | ±2.3 | ±2.8 | ±2.1 | ±2.0 | ±3.0 | ±3.2 | ±2.6 | ±2.4 | ±2.2 | ±2.6 | |
| | 0.5 mg/kg | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | | Mean | 16.6 | 16.3 | 15.5 | 15.2 | 15.2 | 15.4 | 15.0 | 15.2 | 14.9 | 12.6 | |
| | | S.D. | ±1.7 | ±2.8 | ±2.2 | ±1.5 | ±1.9 | ±3.1 | ±2.5 | ±2.4 | ±2.4 | ±2.6 | |
| | 2.5 mg/kg | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | | Mean | 16.4 | 16.7 | 15.5 | 15.4 | 16.1 | 16.2 | 14.8 | 16.0 | 14.6 | 12.9 | |
| | | S.D. | ±1.7 | ±1.8 | ±2.3 | ±1.9 | ±1.9 | ±2.0 | ±3.2 | ±2.2 | ±1.8 | ±2.4 | |
| | 12.5 mg/kg | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | |
| | | Mean | 16.5 | 17.1 | 16.3 | 15.4 | 15.8 | 16.0 | 14.8 | 16.0 | 14.9 | 14.2 | |
| | | S.D. | ±1.8 | ±2.1 | ±2.2 | ±2.4 | ±2.9 | ±2.6 | ±1.8 | ±2.7 | ±2.3 | ±3.0 | |

*: P<0.05 (significantly different from control).

Table 4 - continued Food consumption
Male, Female

| Sex | Group and dose | | Food consumption(g) on day | | | | | | | | | |
|--------|----------------|------|----------------------------|--------|------|------|------|-------|------|------|-------|--------|
| | | | 71 | 78 | 85 | 91 | 92 | 120 | 148 | 176 | 204 | 232 |
| Male | Control | N | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 20.0 | 21.0 | 20.9 | 20.7 | 20.9 | 20.8 | 20.7 | 21.7 | 20.1 | 16.5 |
| | | S.D. | ±2.6 | ±3.2 | ±4.0 | ±3.1 | ±3.9 | ±3.4 | ±4.3 | ±4.0 | ±3.0 | ±2.1 |
| | 0.1 mg/kg | N | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 9 |
| | | Mean | 19.4 | 21.5 | 20.6 | 19.9 | 19.6 | 19.1 | 20.6 | 19.8 | 18.9 | 17.3 |
| | | S.D. | ±2.7 | ±2.4 | ±2.3 | ±2.9 | ±3.2 | ±4.6 | ±3.0 | ±2.2 | ±3.4 | ±2.3 |
| | 0.5 mg/kg | N | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 22.5* | 23.8** | 22.1 | 22.2 | 21.1 | 22.0 | 23.7 | 23.0 | 22.9 | 19.4* |
| | | S.D. | ±2.3 | ±2.4 | ±2.8 | ±2.1 | ±5.9 | ±2.1 | ±2.5 | ±1.9 | ±1.9 | ±1.7 |
| | 2.5 mg/kg | N | 19 | 19 | 19 | 19 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 21.4 | 22.4 | 21.8 | 21.3 | 23.4 | 25.1* | 24.5 | 24.3 | 23.8* | 21.5** |
| | | S.D. | ±2.9 | ±3.1 | ±3.2 | ±2.1 | ±2.7 | ±3.3 | ±5.7 | ±4.4 | ±3.4 | ±3.3 |
| Female | Control | N | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 14.1 | 14.6 | 14.4 | 15.5 | 13.4 | 13.2 | 14.0 | 15.2 | 13.5 | 12.2 |
| | | S.D. | ±2.8 | ±3.7 | ±2.9 | ±2.5 | ±2.8 | ±2.3 | ±2.8 | ±3.7 | ±3.0 | ±3.2 |
| | 0.5 mg/kg | N | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 13.3 | 15.2 | 14.0 | 13.7 | 13.9 | 13.8 | 15.0 | 14.6 | 13.8 | 12.0 |
| | | S.D. | ±2.5 | ±2.0 | ±2.0 | ±2.9 | ±1.6 | ±2.0 | ±2.3 | ±1.7 | ±2.1 | ±2.6 |
| | 2.5 mg/kg | N | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 12.5 | 15.4 | 14.3 | 14.5 | 14.4 | 14.2 | 14.7 | 15.1 | 13.5 | 12.1 |
| | | S.D. | ±1.8 | ±1.9 | ±2.1 | ±2.9 | ±2.0 | ±1.9 | ±1.7 | ±3.0 | ±2.5 | ±2.4 |
| | 12.5 mg/kg | N | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 13.6 | 15.5 | 14.1 | 14.9 | 13.8 | 13.9 | 16.1 | 15.4 | 15.0 | 12.5 |
| | | S.D. | ±2.2 | ±2.2 | ±2.5 | ±2.5 | ±2.3 | ±3.2 | ±2.6 | ±2.2 | ±2.4 | ±2.4 |

*: P<0.05, **: P<0.01 (significantly different from control).

Table 4 - continued Food consumption
Male, Female

| Sex | Group and dose | | Food consumption(g) on day | | | | |
|--------|----------------|------|----------------------------|--------|------|-------|--------|
| | | | 260 | 288 | 316 | 344 | 364 |
| Male | Control | N | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 17.4 | 17.5 | 18.5 | 19.4 | 14.9 |
| | | S.D. | ±2.0 | ±3.5 | ±3.3 | ±5.0 | ±3.9 |
| | 0.1 mg/kg | N | 9 | 9 | 9 | 9 | 8 |
| | | Mean | 17.3 | 16.1 | 15.9 | 14.1* | 13.8 |
| | | S.D. | ±3.3 | ±2.2 | ±2.6 | ±4.5 | ±4.3 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 19.9 | 20.1 | 19.0 | 20.5 | 17.7 |
| | | S.D. | ±2.8 | ±2.2 | ±3.4 | ±3.6 | ±2.1 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 22.0** | 23.1** | 21.5 | 22.5 | 20.8** |
| | | S.D. | ±2.1 | ±3.3 | ±3.5 | ±3.9 | ±2.5 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 13.3 | 12.7 | 12.4 | 13.9 | 12.0 |
| | | S.D. | ±3.5 | ±3.1 | ±2.7 | ±1.8 | ±1.9 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 12.8 | 13.9 | 14.7 | 14.0 | 13.4 |
| | | S.D. | ±2.1 | ±2.5 | ±1.6 | ±2.3 | ±1.1 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 13.8 | 11.5 | 14.5 | 15.2 | 13.2 |
| | | S.D. | ±2.7 | ±1.4 | ±2.1 | ±2.2 | ±1.5 |
| | 12.5 mg/kg | N | 10 | 10 | 10 | 10 | 9 |
| | | Mean | 14.8 | 12.4 | 14.2 | 15.2 | 14.0* |
| | | S.D. | ±2.8 | ±1.8 | ±2.9 | ±5.0 | ±2.0 |

*: P<0.05, **: P<0.01 (significantly different from control).

Table 5 Urinary findings
Male, Female, 13w

| Sex | Group and dose | | Urine volume | Osmotic pressure | Specific gravity | Na | K | Cl |
|--------|----------------|------|--------------|------------------|------------------|------------|------------|------------|
| | | | (mL/24hr) | (Osm/kg) | | (mEq/24hr) | (mEq/24hr) | (mEq/24hr) |
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 14.1 | 1.468 | 1.050 | 0.990 | 2.103 | 1.302 |
| | | S.D. | ±8.7 | ±0.661 | ±0.022 | ±0.357 | ±0.295 | ±0.380 |
| | 0.1 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 15.6 | 1.157 | 1.040 | 1.042 | 2.123 | 1.444 |
| | | S.D. | ±5.5 | ±0.362 | ±0.012 | ±0.372 | ±0.531 | ±0.440 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 10.6 | 1.861 | 1.062 | 0.984 | 2.134 | 1.320 |
| | | S.D. | ±2.9 | ±0.417 | ±0.014 | ±0.236 | ±0.282 | ±0.198 |
| | 2.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Mean | 7.8 | 2.197** | 1.072** | 1.147 | 1.909 | 1.268 |
| | | S.D. | ±1.8 | ±0.382 | ±0.011 | ±0.296 | ±0.372 | ±0.300 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 8.5 | 1.602 | 1.051 | 0.782 | 1.659 | 1.143 |
| | | S.D. | ±5.2 | ±0.637 | ±0.019 | ±0.323 | ±0.761 | ±0.470 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 8.7 | 1.234 | 1.040 | 0.599 | 1.390 | 0.878 |
| | | S.D. | ±2.7 | ±0.219 | ±0.008 | ±0.250 | ±0.488 | ±0.345 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 10.0 | 1.185 | 1.039 | 0.661 | 1.607 | 0.973 |
| | | S.D. | ±3.3 | ±0.285 | ±0.009 | ±0.296 | ±0.495 | ±0.285 |
| | 12.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 7.8 | 1.558 | 1.051 | 0.655 | 1.506 | 0.952 |
| | | S.D. | ±2.8 | ±0.506 | ±0.016 | ±0.195 | ±0.444 | ±0.305 |

** : P<0.01 (significantly different from control).

Table 5 - continued

Urinary findings
Male, Female, 13w

| Sex | Group and dose | Number of animals | Color | | pH | | | | | | | Protein | | | | Glucose |
|--------|----------------|-------------------|-------|----|-----|-----|-----|-----|-----|-----|-----|---------|---|---|----|---------|
| | | | PY | Y. | 5.5 | 6.0 | 6.5 | 7.0 | 7.5 | 8.0 | 8.5 | - | ± | + | ++ | - |
| Male | Control | 10 | 3 | 7 | 0 | 0 | 0 | 1 | 2 | 6 | 1 | 1 | 5 | 4 | 0 | 10 |
| | 0.1 mg/kg | 10 | 3 | 7 | 1 | 0 | 0 | 0 | 0 | 6 | 3 | 1 | 4 | 5 | 0 | 10 |
| | 0.5 mg/kg | 10 | 0 | 10 | 0 | 0 | 0 | 0 | 1 | 9 | 0 | 2 | 2 | 5 | 1 | 10 |
| | 2.5 mg/kg | 9 | 0 | 9 | 0 | 0 | 0 | 0 | 1 | 5 | 3 | 1 | 4 | 2 | 2 | 9 |
| Female | Control | 10 | 0 | 10 | 0 | 1 | 1 | 1 | 1 | 5 | 1 | 8 | 0 | 2 | 0 | 10 |
| | 0.5 mg/kg | 10 | 0 | 10 | 0 | 0 | 0 | 1 | 1 | 2 | 6 | 10 | 0 | 0 | 0 | 10 |
| | 2.5 mg/kg | 10 | 0 | 10 | 0 | 2 | 0 | 0 | 2 | 3 | 3 | 8 | 2 | 0 | 0 | 10 |
| | 12.5 mg/kg | 10 | 0 | 10 | 0 | 0 | 0 | 0 | 3 | 5 | 2 | 7 | 3 | 0 | 0 | 10 |

Not significantly different from control.

Abbreviation: PY, pale yellow; Y, yellow.

Grade sign: -, none; ±, trace; +, slight; ++, moderate; +++, severe; +++++, very severe.

Table 5 - continued
Urinary findings
Male, Female, 13w

| Sex | Group and dose | Number of animals | Ketone body | | Bilirubin | | Occult blood | | Urobilinogen (mg/dL) |
|--------|----------------|-------------------|-------------|----|-----------|-----|--------------|-----|----------------------|
| | | | - | - | - | +++ | - | +++ | <1 |
| Male | Control | 10 | 10 | 10 | 10 | 0 | 10 | 10 | |
| | 0.1 mg/kg | 10 | 10 | 10 | 10 | 0 | 10 | 10 | |
| | 0.5 mg/kg | 10 | 10 | 10 | 10 | 0 | 10 | 10 | |
| | 2.5 mg/kg | 9 | 9 | 9 | 8 | 1 | 9 | 9 | |
| Female | Control | 10 | 10 | 10 | 10 | 0 | 10 | 10 | |
| | 0.5 mg/kg | 10 | 10 | 10 | 10 | 0 | 10 | 10 | |
| | 2.5 mg/kg | 10 | 10 | 10 | 10 | 0 | 10 | 10 | |
| | 12.5 mg/kg | 10 | 10 | 10 | 10 | 0 | 10 | 10 | |

Not significantly different from control.
Grade sign: -, none; ±, trace; +, slight; ++, moderate; +++, severe.

Table 5 - continued
Urinary findings
Male, Female, 13w

| Sex | Group and dose | Number of animals | Urinary sediment | | | | | | | | | | |
|--------|----------------|-------------------|------------------|----|--------------|-----|------------|----|-------|----------|---|----|-----|
| | | | Epithelial cells | | Erythrocytes | | Leukocytes | | Casts | Crystals | | | |
| | | | - | - | - | +++ | - | + | - | - | + | ++ | +++ |
| Male | Control | 10 | 10 | 10 | 0 | 10 | 0 | 10 | 7 | 0 | 2 | 1 | |
| | 0.1 mg/kg | 10 | 10 | 10 | 0 | 10 | 0 | 10 | 9 | 1 | 0 | 0 | |
| | 0.5 mg/kg | 10 | 10 | 10 | 0 | 9 | 1 | 10 | 5 | 2 | 0 | 3 | |
| | 2.5 mg/kg | 9 | 9 | 8 | 1 | 9 | 0 | 9 | 8 | 0 | 1 | 0 | |
| Female | Control | 10 | 10 | 10 | 0 | 10 | 0 | 10 | 10 | 0 | 0 | 0 | |
| | 0.5 mg/kg | 10 | 10 | 10 | 0 | 10 | 0 | 10 | 10 | 0 | 0 | 0 | |
| | 2.5 mg/kg | 10 | 10 | 10 | 0 | 10 | 0 | 10 | 10 | 0 | 0 | 0 | |
| | 12.5 mg/kg | 10 | 10 | 10 | 0 | 10 | 0 | 10 | 10 | 0 | 0 | 0 | |

Not significantly different from control.

Grade signs are as follows.

Epithelial cells: -, < 3/field; +, 3/field \leq and < 10/field; ++, 10/field \leq and < 20/field; +++, \geq 20/field.
 Erythrocytes : -, < 10/field; +, 10/field \leq and < 30/field; ++, 30/field \leq and < 100/field; +++, countless.
 Leukocytes : -, < 3/field; +, 3/field \leq and < 20/field; ++, 20/field \leq and < 40/field; +++, \geq 40/field.
 Casts : -, none; +, \geq 1/all field.
 Crystals : -, < 10/field; +, 10/field \leq and < 20/field; ++, 20/field \leq and < 30/field; +++, countless.

Table 6 Urinary findings
Male, Female, 52w

| Sex | Group and dose | | Urine volume (mL/24hr) | Osmotic pressure (Osm/kg) | Specific gravity | Na (mEq/24hr) | K (mEq/24hr) | Cl (mEq/24hr) |
|--------|----------------|-------|---------------------------|------------------------------|------------------|------------------|-----------------|------------------|
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 9.3 | 1.316 | 1.047 | 0.663 | 1.501 | 0.774 |
| | | S. D. | ±3.3 | ±0.305 | ±0.013 | ±0.468 | ±0.480 | ±0.522 |
| | 0.1 mg/kg | N | 8 | 8 | 8 | 8 | 8 | 8 |
| | | Mean | 7.9 | 1.556 | 1.056 | 0.546 | 1.376 | 0.566 |
| | | S. D. | ±3.0 | ±0.330 | ±0.013 | ±0.299 | ±0.270 | ±0.306 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 9.1 | 1.910** | 1.065* | 0.822 | 1.801 | 0.911 |
| | | S. D. | ±2.5 | ±0.418 | ±0.016 | ±0.373 | ±0.286 | ±0.394 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 8.6 | 1.809* | 1.061 | 0.870 | 1.517 | 0.831 |
| | | S. D. | ±2.2 | ±0.417 | ±0.013 | ±0.461 | ±0.413 | ±0.353 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 9.9 | 1.325 | 1.046 | 0.727 | 1.836 | 1.043 |
| | | S. D. | ±5.0 | ±0.352 | ±0.013 | ±0.425 | ±0.648 | ±0.505 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 12.6 | 1.200 | 1.042 | 0.730 | 1.753 | 1.019 |
| | | S. D. | ±7.3 | ±0.509 | ±0.017 | ±0.251 | ±0.226 | ±0.263 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 14.7 | 1.043 | 1.037 | 0.722 | 1.780 | 1.077 |
| | | S. D. | ±8.7 | ±0.432 | ±0.018 | ±0.309 | ±0.393 | ±0.346 |
| | 12.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Mean | 19.0* | 0.840* | 1.030 | 0.999 | 2.167 | 1.315 |
| | | S. D. | ±9.0 | ±0.219 | ±0.008 | ±0.256 | ±0.418 | ±0.308 |

*: P<0.05, **: P<0.01 (significantly different from control).

Table 6 - continued

Urinary findings
Male, Female, 52w

| Sex | Group and dose | Number of animals | Color | | pH | | | | | | | Protein | | | | | | Glucose |
|--------|----------------|-------------------|-------|----|-----|-----|-----|-----|-----|-----|-----|---------|---|---|----|-----|------|---------|
| | | | PY | Y | 5.5 | 6.0 | 6.5 | 7.0 | 7.5 | 8.0 | 8.5 | - | ± | + | ++ | +++ | ++++ | - |
| Male | Control | 10 | 2 | 8 | 1 | 0 | 0 | 1 | 3 | 4 | 1 | 2 | 0 | 3 | 5 | 0 | 0 | 10 |
| | 0.1 mg/kg | 8 | 0 | 8 | 0 | 0 | 0 | 1 | 1 | 6 | 0 | 0 | 2 | 5 | 1 | 0 | 0 | 8 |
| | 0.5 mg/kg | 10 | 0 | 10 | 2 | 2 | 3 | 0 | 1 | 2 | 0 | 0 | 1 | 3 | 3 | 2 | 1 | 10 |
| | 2.5 mg/kg | 10 | 0 | 10 | 0 | 2 | 0 | 1 | 1 | 4 | 2 | 0 | 1 | 5 | 3 | 1 | 0 | 10 |
| Female | Control | 10 | 0 | 10 | 2 | 0 | 0 | 0 | 1 | 3 | 4 | 6 | 2 | 2 | 0 | 0 | 0 | 10 |
| | 0.5 mg/kg | 10 | 1 | 9 | 1 | 1 | 1 | 1 | 1 | 4 | 1 | 6 | 1 | 3 | 0 | 0 | 0 | 10 |
| | 2.5 mg/kg | 10 | 3 | 7 | 2 | 0 | 3 | 1 | 1 | 2 | 1 | 5 | 1 | 3 | 1 | 0 | 0 | 10 |
| | 12.5 mg/kg | 9 | 2 | 7 | 1 | 1 | 3 | 1 | 1 | 2 | 0 | 3 | 4 | 2 | 0 | 0 | 0 | 9 |

Not significantly different from control.

Abbreviation: PY, pale yellow; Y, yellow; YB, yellowish brown; B, brown.

Grade sign: -, none; ±, trace; +, slight; ++, moderate; +++, severe; +++++, very severe.

Table 6 - continued

Urinary findings
Male, Female, 52w

| Sex | Group and dose | Number of animals | Ketone body | Bilirubin | Occult blood | | | Urobilinogen (mg/dL) |
|--------|----------------|-------------------|-------------|-----------|--------------|----|-----|----------------------|
| | | | - | - | - | ++ | +++ | <1 |
| Male | Control | 10 | 10 | 10 | 9 | 1 | 0 | 10 |
| | 0.1 mg/kg | 8 | 8 | 8 | 7 | 0 | 1 | 8 |
| | 0.5 mg/kg | 10 | 10 | 10 | 9 | 0 | 1 | 10 |
| | 2.5 mg/kg | 10 | 10 | 10 | 10 | 0 | 0 | 10 |
| Female | Control | 10 | 10 | 10 | 10 | 0 | 0 | 10 |
| | 0.5 mg/kg | 10 | 10 | 10 | 10 | 0 | 0 | 10 |
| | 2.5 mg/kg | 10 | 10 | 10 | 10 | 0 | 0 | 10 |
| | 12.5 mg/kg | 9 | 9 | 9 | 9 | 0 | 0 | 9 |

Not significantly different from control.

Grade sign: -, none; ±, trace; +, slight; ++, moderate; +++, severe; +++++, very severe.

Table 6 - continued
Urinary findings
Male, Female, 52w

| Sex | Group and dose | Number of animals | Urinary sediment | | | | | | | | | |
|--------|----------------|-------------------|------------------|---|--------------|---|------------|---|-------|----------|---|-----|
| | | | Epithelial cells | | Erythrocytes | | Leukocytes | | Casts | Crystals | | |
| | | | - | + | - | + | - | + | - | - | + | +++ |
| Male | Control | 10 | 10 | 0 | 10 | 0 | 9 | 1 | 10 | 10 | 0 | 0 |
| | 0.1 mg/kg | 8 | 8 | 0 | 8 | 0 | 7 | 1 | 8 | 7 | 0 | 1 |
| | 0.5 mg/kg | 10 | 10 | 1 | 9 | 1 | 9 | 1 | 10 | 9 | 1 | 0 |
| | 2.5 mg/kg | 10 | 10 | 0 | 10 | 0 | 10 | 0 | 10 | 9 | 1 | 0 |
| Female | Control | 10 | 10 | 0 | 10 | 0 | 10 | 0 | 10 | 9 | 1 | 0 |
| | 0.5 mg/kg | 10 | 10 | 0 | 10 | 0 | 10 | 0 | 10 | 8 | 2 | 0 |
| | 2.5 mg/kg | 10 | 10 | 0 | 10 | 0 | 10 | 0 | 10 | 10 | 0 | 0 |
| | 12.5 mg/kg | 9 | 9 | 0 | 9 | 0 | 9 | 0 | 9 | 9 | 0 | 0 |

Not significantly different from control.

Grade signs are as follows.

Epithelial cells: -, < 3/field; +, 3/field \leq and < 10/field; ++, 10/field \leq and < 20/field; +++, \geq 20/field.
 Erythrocytes : -, < 10/field; +, 10/field \leq and < 30/field; ++, 30/field \leq and < 100/field; +++, countless.
 Leukocytes : -, < 3/field; +, 3/field \leq and < 20/field; ++, 20/field \leq and < 40/field; +++, \geq 40/field.
 Casts : -, none; +, \geq 1/all field.
 Crystals : -, < 10/field; +, 10/field \leq and < 20/field; ++, 20/field \leq and < 30/field; +++, countless.

Table 7 Hematological findings
Male, Female, 13w

| Sex | Group and dose | | Leukocytes ($10^3 / \mu\text{L}$) | Erythrocytes ($10^4 / \mu\text{L}$) | Hemoglobin (g/dL) | Hematocrit (%) | MCV (fL) | MCH (pg) | MCHC (g/dL) | Reticulocyte ($10^4 / \mu\text{L}$) | Platelets ($10^4 / \mu\text{L}$) |
|--------|----------------|------|--|--|----------------------|-------------------|-------------|-------------|----------------|--|---------------------------------------|
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 7.83 | 855 | 15.6 | 43.3 | 50.6 | 18.3 | 36.1 | 15.8 | 103.4 |
| | | S.D. | ± 1.32 | ± 27 | ± 0.4 | ± 1.6 | ± 1.6 | ± 0.5 | ± 0.7 | ± 2.8 | ± 11.2 |
| | 0.1 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 8.63 | 870 | 15.5 | 43.2 | 49.6 | 17.8 | 35.9 | 16.3 | 108.7 |
| | | S.D. | ± 2.72 | ± 29 | ± 0.5 | ± 1.2 | ± 1.1 | ± 0.5 | ± 0.4 | ± 1.8 | ± 8.2 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 9.08 | 828 | 15.0* | 41.6* | 50.3 | 18.1 | 36.0 | 16.2 | 112.9 |
| | | S.D. | ± 2.48 | ± 43 | ± 0.6 | ± 1.8 | ± 0.9 | ± 0.5 | ± 0.7 | ± 3.2 | ± 16.0 |
| | 2.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Mean | 9.97 | 807** | 14.3** | 40.0** | 49.6 | 17.7 | 35.7 | 14.8 | 130.5* |
| | | S.D. | ± 1.88 | ± 22 | ± 0.6 | ± 1.3 | ± 2.6 | ± 1.0 | ± 0.5 | ± 3.6 | ± 27.1 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 4.94 | 768 | 13.9 | 40.1 | 52.2 | 18.1 | 34.6 | 16.5 | 106.1 |
| | | S.D. | ± 1.16 | ± 38 | ± 0.5 | ± 1.7 | ± 1.1 | ± 0.4 | ± 0.5 | ± 3.4 | ± 12.1 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 4.30 | 793 | 14.1 | 40.7 | 51.3 | 17.7 | 34.6 | 13.9 | 110.4 |
| | | S.D. | ± 1.04 | ± 40 | ± 0.6 | ± 2.2 | ± 0.7 | ± 0.4 | ± 0.6 | ± 1.9 | ± 6.8 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 4.95 | 762 | 13.8 | 39.5 | 51.9 | 18.1 | 35.0 | 14.8 | 117.4 |
| | | S.D. | ± 0.99 | ± 23 | ± 0.4 | ± 0.9 | ± 1.3 | ± 0.5 | ± 0.3 | ± 3.4 | ± 11.6 |
| | 12.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 5.18 | 753 | 13.4 | 38.1* | 50.6** | 17.7 | 35.1* | 13.7 | 106.2 |
| | | S.D. | ± 1.70 | ± 25 | ± 0.5 | ± 1.2 | ± 1.0 | ± 0.5 | ± 0.5 | ± 1.6 | ± 9.9 |

*: $P < 0.05$, **: $P < 0.01$ (significantly different from control).

Table 7 - continued
Hematological findings
Male, Female, 13w

| Sex | Group and dose | | PT (sec) | APTT (sec) |
|--------|----------------|------|-------------|---------------|
| Male | Control | N | 10 | 10 |
| | | Mean | 15.2 | 24.6 |
| | | S.D. | ±2.7 | ±1.9 |
| | 0.1 mg/kg | N | 10 | 10 |
| | | Mean | 14.9 | 24.1 |
| | | S.D. | ±1.1 | ±1.9 |
| | 0.5 mg/kg | N | 10 | 10 |
| | | Mean | 15.1 | 23.0 |
| | | S.D. | ±1.5 | ±1.5 |
| | 2.5 mg/kg | N | 9 | 9 |
| | | Mean | 14.3 | 23.5 |
| | | S.D. | ±1.4 | ±3.1 |
| Female | Control | N | 10 | 10 |
| | | Mean | 11.7 | 19.2 |
| | | S.D. | ±0.5 | ±1.5 |
| | 0.5 mg/kg | N | 10 | 10 |
| | | Mean | 11.7 | 19.7 |
| | | S.D. | ±0.3 | ±0.9 |
| | 2.5 mg/kg | N | 10 | 10 |
| | | Mean | 11.7 | 19.0 |
| | | S.D. | ±0.3 | ±1.6 |
| | 12.5 mg/kg | N | 10 | 10 |
| | | Mean | 11.8 | 19.2 |
| | | S.D. | ±0.4 | ±1.5 |

Not significantly different from control.

Table 7 - continued
Hematological findings
Male, Female, 13w

| Sex | Group and dose | | Differential leukocyte count | | | | | |
|--------|----------------|-------|------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| | | | Eosinophils | Neutrophils | Lymphocytes | Basophils | Monocytes | Large unstained cells |
| | | | (10 ² / μ L) | (10 ² / μ L) | (10 ² / μ L) | (10 ² / μ L) | (10 ² / μ L) | (10 ² / μ L) |
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.2 | 16.2 | 58.7 | 0.1 | 1.7 | 0.3 |
| | | S. D. | ± 0.6 | ± 6.1 | ± 14.3 | ± 0.1 | ± 0.5 | ± 0.1 |
| | 0.1 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.4 | 16.8 | 65.5 | 0.2 | 1.8 | 0.5 |
| | | S. D. | ± 0.4 | ± 9.8 | ± 23.5 | ± 0.1 | ± 0.7 | ± 0.4 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.3 | 13.8 | 72.9 | 0.2 | 2.0 | 0.7* |
| | | S. D. | ± 0.7 | ± 5.1 | ± 21.7 | ± 0.1 | ± 1.0 | ± 0.3 |
| | 2.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Mean | 1.1 | 14.4 | 81.1 | 0.2 | 2.2 | 0.7 |
| | | S. D. | ± 0.4 | ± 5.5 | ± 19.9 | ± 0.1 | ± 0.7 | ± 0.5 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.9 | 7.1 | 40.1 | 0.1 | 0.8 | 0.4 |
| | | S. D. | ± 0.4 | ± 2.7 | ± 9.5 | ± 0.1 | ± 0.3 | ± 0.2 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.8 | 6.3 | 34.9 | 0.1 | 0.7 | 0.3 |
| | | S. D. | ± 0.5 | ± 1.6 | ± 8.5 | ± 0.1 | ± 0.3 | ± 0.1 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.8 | 8.3 | 39.4 | 0.1 | 0.6 | 0.4 |
| | | S. D. | ± 0.3 | ± 3.8 | ± 8.7 | ± 0.0 | ± 0.2 | ± 0.2 |
| | 12.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.9 | 6.2 | 43.5 | 0.1 | 0.8 | 0.3 |
| | | S. D. | ± 0.3 | ± 2.2 | ± 15.2 | ± 0.1 | ± 0.4 | ± 0.2 |

*: P<0.05 (significantly different from control).

Table 8 Hematological findings
Male, Female, 52w

| Sex | Group and dose | | Leukocytes | Erythrocytes | Hemoglobin | Hematocrit | MCV | MCH | MCHC | Reticulocyte | Platelets |
|--------|----------------|-------|--------------------------|--------------------------|------------|------------|-----------|-----------|-----------|--------------------------|--------------------------|
| | | | ($10^3 / \mu\text{L}$) | ($10^4 / \mu\text{L}$) | (g/dL) | (%) | (fL) | (pg) | (g/dL) | ($10^4 / \mu\text{L}$) | ($10^4 / \mu\text{L}$) |
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 7.98 | 840 | 14.0 | 44.2 | 52.7 | 16.7 | 31.7 | 18.2 | 106.5 |
| | | S. D. | ± 1.24 | ± 68 | ± 1.1 | ± 2.9 | ± 2.1 | ± 0.8 | ± 0.8 | ± 8.4 | ± 12.6 |
| | 0.1 mg/kg | N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | | Mean | 8.22 | 780 | 13.1 | 41.3 | 53.1 | 16.7 | 31.5 | 20.1 | 110.2 |
| | | S. D. | ± 3.46 | ± 145 | ± 2.7 | ± 7.4 | ± 1.2 | ± 0.7 | ± 1.5 | ± 9.8 | ± 28.5 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 6.69 | 754* | 12.7 | 40.3 | 53.9 | 16.9 | 31.3 | 27.1 | 123.7 |
| | | S. D. | ± 0.98 | ± 133 | ± 2.1 | ± 5.7 | ± 4.5 | ± 1.0 | ± 1.1 | ± 20.4 | ± 28.5 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 7.90 | 778* | 12.9 | 40.7* | 52.3 | 16.6 | 31.8 | 15.7 | 140.1** |
| | | S. D. | ± 2.19 | ± 66 | ± 1.1 | ± 3.6 | ± 2.3 | ± 0.7 | ± 0.3 | ± 3.3 | ± 13.6 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 3.83 | 707 | 13.2 | 40.3 | 57.5 | 18.8 | 32.7 | 14.9 | 90.2 |
| | | S. D. | ± 1.30 | ± 100 | ± 1.4 | ± 3.8 | ± 4.3 | ± 1.0 | ± 0.9 | ± 8.9 | ± 10.0 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 3.73 | 708 | 13.5 | 41.0 | 58.1 | 19.1 | 33.0 | 16.4 | 94.2 |
| | | S. D. | ± 0.96 | ± 62 | ± 0.8 | ± 2.5 | ± 2.3 | ± 0.7 | ± 0.5 | ± 9.6 | ± 14.7 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 3.98 | 730 | 13.5 | 41.3 | 56.6 | 18.5 | 32.7 | 13.9 | 101.5 |
| | | S. D. | ± 1.44 | ± 55 | ± 1.0 | ± 3.0 | ± 2.4 | ± 0.8 | ± 0.6 | ± 5.8 | ± 13.9 |
| | 12.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Mean | 3.69 | 673 | 12.3 | 37.3 | 56.1 | 18.4 | 32.9 | 17.1 | 105.6* |
| | | S. D. | ± 0.58 | ± 115 | ± 1.5 | ± 4.4 | ± 4.8 | ± 1.4 | ± 0.4 | ± 15.1 | ± 11.9 |

*: $P < 0.05$, **: $P < 0.01$ (significantly different from control).

Table 8 - continued
Hematological findings
Male, Female, 52w

| Sex | Group and dose | | PT (sec) | APTT (sec) |
|--------|----------------|------|-------------|---------------|
| Male | Control | N | 10 | 10 |
| | | Mean | 13.5 | 21.5 |
| | | S.D. | ±1.0 | ±1.5 |
| | 0.1 mg/kg | N | 8 | 8 |
| | | Mean | 13.8 | 20.9 |
| | | S.D. | ±1.0 | ±2.7 |
| | 0.5 mg/kg | N | 10 | 10 |
| | | Mean | 14.5 | 21.2 |
| | | S.D. | ±1.9 | ±2.6 |
| | 2.5 mg/kg | N | 10 | 10 |
| | | Mean | 21.8** | 29.5 |
| | | S.D. | ±9.0 | ±9.3 |
| Female | Control | N | 10 | 10 |
| | | Mean | 12.3 | 18.4 |
| | | S.D. | ±0.8 | ±0.9 |
| | 0.5 mg/kg | N | 10 | 10 |
| | | Mean | 12.9 | 18.5 |
| | | S.D. | ±0.7 | ±0.9 |
| | 2.5 mg/kg | N | 10 | 10 |
| | | Mean | 12.5 | 17.7 |
| | | S.D. | ±0.5 | ±1.4 |
| | 12.5 mg/kg | N | 9 | 9 |
| | | Mean | 12.1 | 17.7 |
| | | S.D. | ±0.5 | ±1.2 |

**; P<0.01 (significantly different from control).

Table 8 - continued
Hematological findings
Male, Female, 52w

| Sex | Group and dose | | Differential leukocyte count | | | | | |
|--------|----------------|------|------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| | | | Eosinophils | Neutrophils | Lymphocytes | Basophils | Monocytes | Large unstained cells |
| | | | (10 ² / μ L) | (10 ² / μ L) | (10 ² / μ L) | (10 ² / μ L) | (10 ² / μ L) | (10 ² / μ L) |
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.2 | 26.2 | 47.8 | 0.1 | 3.0 | 1.5 |
| | | S.D. | ± 0.3 | ± 9.9 | ± 11.9 | ± 0.0 | ± 0.9 | ± 2.0 |
| | 0.1 mg/kg | N | 8 | 8 | 8 | 8 | 8 | 8 |
| | | Mean | 1.0 | 30.8 | 46.4 | 0.1 | 2.5 | 1.5 |
| | | S.D. | ± 0.6 | ± 29.1 | ± 6.5 | ± 0.1 | ± 0.5 | ± 2.4 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.9 | 18.6 | 44.3 | 0.1 | 2.3 | 0.7 |
| | | S.D. | ± 0.3 | ± 7.3 | ± 6.3 | ± 0.0 | ± 0.7 | ± 0.2 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.1 | 17.6 | 56.2 | 0.1 | 2.9 | 1.1 |
| | | S.D. | ± 0.5 | ± 7.5 | ± 17.5 | ± 0.1 | ± 0.8 | ± 0.7 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.6 | 10.1 | 25.4 | 0.0 | 1.4 | 0.7 |
| | | S.D. | ± 0.2 | ± 8.0 | ± 8.2 | ± 0.0 | ± 0.8 | ± 0.3 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.7 | 11.0 | 23.3 | 0.0 | 1.6 | 0.6 |
| | | S.D. | ± 0.2 | ± 4.0 | ± 7.2 | ± 0.0 | ± 0.5 | ± 0.3 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.9 | 12.1 | 24.6 | 0.0 | 1.6 | 0.6 |
| | | S.D. | ± 0.4 | ± 6.7 | ± 8.2 | ± 0.0 | ± 0.6 | ± 0.3 |
| | 12.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Mean | 0.8 | 9.2 | 24.8 | 0.0 | 1.6 | 0.5 |
| | | S.D. | ± 0.2 | ± 1.9 | ± 6.3 | ± 0.0 | ± 0.5 | ± 0.2 |

Not significantly different from control.

Table 9 Biochemical findings
Male, Female, 13w

| Sex | Group and dose | | T.Protein | A/G ratio | α_1 -Globulin | α_2 -Globulin | β -Globulin | γ -Globulin | Albumin |
|--------|----------------|------|-----------|-----------|----------------------|----------------------|-------------------|--------------------|---------|
| | | | (g/dL) | | (%) | (%) | (%) | (%) | (%) |
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 5.8 | 1.22 | 18.7 | 7.1 | 15.2 | 4.2 | 54.8 |
| | | S.D. | ±0.3 | ±0.12 | ±1.6 | ±0.7 | ±0.8 | ±0.5 | ±2.3 |
| | 0.1 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 5.8 | 1.30 | 17.9 | 6.8 | 14.4 | 4.3 | 56.6 |
| | | S.D. | ±0.2 | ±0.09 | ±1.6 | ±0.6 | ±0.6 | ±0.6 | ±1.6 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 5.7 | 1.67** | 15.6** | 5.9** | 11.5** | 4.6 | 62.4** |
| | | S.D. | ±0.5 | ±0.23 | ±1.3 | ±0.6 | ±1.0 | ±0.8 | ±2.9 |
| | 2.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Mean | 5.8 | 2.09** | 12.1** | 5.6** | 9.9** | 5.0 | 67.4** |
| | | S.D. | ±0.5 | ±0.27 | ±2.4 | ±0.6 | ±0.7 | ±1.4 | ±3.0 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 6.2 | 1.78 | 13.8 | 5.6 | 12.6 | 3.9 | 64.0 |
| | | S.D. | ±0.4 | ±0.16 | ±1.0 | ±0.8 | ±0.9 | ±0.8 | ±2.0 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 6.3 | 1.87 | 12.9 | 5.6 | 12.4 | 4.3 | 64.9 |
| | | S.D. | ±0.2 | ±0.22 | ±1.7 | ±0.2 | ±1.2 | ±1.0 | ±2.8 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 6.4 | 1.93 | 12.6 | 5.5 | 12.1 | 4.2 | 65.7 |
| | | S.D. | ±0.4 | ±0.19 | ±1.6 | ±0.6 | ±1.4 | ±1.0 | ±2.2 |
| | 12.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 6.7* | 2.24** | 12.9 | 4.7* | 9.9** | 3.6 | 68.9** |
| | | S.D. | ±0.5 | ±0.31 | ±1.8 | ±0.5 | ±0.8 | ±1.1 | ±2.9 |

*: P<0.05, **: P<0.01 (significantly different from control).

Table 9 - continued
Biochemical findings
Male, Female, 13w

| Sex | Group and dose | | T.Bilirubin (mg/dL) | AST (IU/L) | ALT (IU/L) | ALP (IU/L) | T.Cholesterol (mg/dL) | Triglycerides (mg/dL) | Phospholipids (mg/dL) | Glucose (mg/dL) |
|--------|----------------|-------|------------------------|---------------|---------------|---------------|--------------------------|--------------------------|--------------------------|--------------------|
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.0 | 90 | 35 | 164 | 68 | 48 | 119 | 121 |
| | | S. D. | ±0.0 | ±22 | ±29 | ±23 | ±12 | ±21 | ±21 | ±9 |
| | 0.1 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.0 | 118 | 47 | 216 | 64 | 43 | 116 | 120 |
| | | S. D. | ±0.0 | ±66 | ±58 | ±57 | ±12 | ±12 | ±23 | ±7 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.0 | 83 | 23 | 373** | 59 | 58 | 125 | 154** |
| | | S. D. | ±0.0 | ±14 | ±4 | ±60 | ±13 | ±29 | ±27 | ±13 |
| | 2.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Mean | 0.0 | 94 | 32 | 619** | 58 | 65 | 131 | 151** |
| | | S. D. | ±0.0 | ±16 | ±9 | ±115 | ±9 | ±19 | ±16 | ±9 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.1 | 75 | 20 | 92 | 75 | 29 | 150 | 119 |
| | | S. D. | ±0.1 | ±20 | ±7 | ±30 | ±12 | ±20 | ±21 | ±13 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.0* | 69 | 18 | 107 | 78 | 24 | 155 | 117 |
| | | S. D. | ±0.0 | ±8 | ±6 | ±25 | ±10 | ±9 | ±15 | ±10 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.0 | 77 | 17 | 101 | 72 | 23 | 147 | 118 |
| | | S. D. | ±0.0 | ±14 | ±2 | ±31 | ±12 | ±10 | ±23 | ±15 |
| | 12.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.0* | 68 | 18 | 136 | 83 | 35 | 169 | 130 |
| | | S. D. | ±0.0 | ±10 | ±2 | ±81 | ±7 | ±13 | ±16 | ±10 |

*: P<0.05, **: P<0.01 (significantly different from control).

Table 9 - continued Biochemical findings
Male, Female, 13w

| Sex | Group and dose | | BUN (mg/dL) | Creatinine (mg/dL) | IP (mg/dL) | Ca (mg/dL) | Na (mEq/L) | K (mEq/L) | Cl (mEq/L) |
|--------|----------------|------|----------------|-----------------------|---------------|---------------|---------------|--------------|---------------|
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 12.3 | 0.4 | 6.1 | 10.2 | 147.1 | 4.14 | 106.5 |
| | | S.D. | ±1.1 | ±0.1 | ±0.6 | ±0.2 | ±0.6 | ±0.13 | ±1.0 |
| | 0.1 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 11.8 | 0.4 | 6.4 | 10.3 | 147.3 | 4.36 | 105.7 |
| | | S.D. | ±1.7 | ±0.0 | ±0.3 | ±0.3 | ±0.7 | ±0.21 | ±1.1 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 14.2* | 0.4 | 6.6 | 10.1 | 145.9* | 4.53** | 105.3 |
| | | S.D. | ±1.7 | ±0.0 | ±0.5 | ±0.4 | ±0.9 | ±0.28 | ±1.8 |
| | 2.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Mean | 14.8** | 0.4 | 6.8* | 10.0 | 144.9** | 4.66** | 105.7 |
| | | S.D. | ±1.8 | ±0.0 | ±0.6 | ±0.3 | ±1.1 | ±0.32 | ±1.7 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 14.5 | 0.5 | 4.9 | 10.4 | 145.7 | 4.02 | 108.6 |
| | | S.D. | ±1.7 | ±0.1 | ±0.6 | ±0.2 | ±0.7 | ±0.17 | ±0.9 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 14.3 | 0.5 | 5.1 | 10.4 | 145.8 | 4.14 | 108.6 |
| | | S.D. | ±1.7 | ±0.1 | ±0.6 | ±0.2 | ±1.1 | ±0.20 | ±1.2 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 13.6 | 0.5 | 5.2 | 10.5 | 145.6 | 3.98 | 108.5 |
| | | S.D. | ±1.1 | ±0.1 | ±0.7 | ±0.4 | ±0.8 | ±0.13 | ±1.7 |
| | 12.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 14.1 | 0.4 | 5.4 | 10.7 | 145.1 | 3.98 | 108.9 |
| | | S.D. | ±1.8 | ±0.1 | ±0.7 | ±0.3 | ±1.1 | ±0.19 | ±1.2 |

*: P<0.05, **: P<0.01 (significantly different from control).

Table 10 Biochemical findings
Male, Female, 52w

| Sex | Group and dose | | T. Protein (g/dL) | A/G ratio | α_1 -Globulin (%) | α_2 -Globulin (%) | β -Globulin (%) | γ -Globulin (%) | Albumin (%) |
|--------|----------------|-------|----------------------|-----------|-----------------------------|-----------------------------|--------------------------|---------------------------|----------------|
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 5.8 | 1.01 | 19.2 | 7.5 | 17.9 | 5.7 | 49.7 |
| | | S. D. | ±0.2 | ±0.21 | ±2.2 | ±0.5 | ±2.3 | ±2.3 | ±5.4 |
| | 0.1 mg/kg | N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | | Mean | 5.8 | 1.01 | 18.2 | 7.1 | 18.5 | 6.9 | 49.3 |
| | | S. D. | ±0.3 | ±0.29 | ±1.8 | ±1.4 | ±4.5 | ±3.1 | ±8.4 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 5.8 | 1.42** | 15.2** | 6.1* | 15.3 | 5.2 | 58.1** |
| | | S. D. | ±0.5 | ±0.31 | ±2.4 | ±1.3 | ±3.0 | ±1.7 | ±5.4 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 5.8 | 1.75** | 13.4** | 5.0** | 12.7** | 5.8 | 63.2** |
| | | S. D. | ±0.2 | ±0.30 | ±2.0 | ±1.1 | ±2.2 | ±1.2 | ±4.7 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 6.4 | 1.79 | 13.5 | 4.8 | 13.2 | 4.6 | 63.9 |
| | | S. D. | ±0.3 | ±0.25 | ±1.6 | ±0.6 | ±1.5 | ±0.9 | ±3.1 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 6.7 | 1.69 | 14.2 | 4.8 | 13.5 | 4.9 | 62.6 |
| | | S. D. | ±0.2 | ±0.17 | ±1.6 | ±0.5 | ±0.7 | ±1.2 | ±2.5 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 6.7 | 1.73 | 12.8 | 5.0 | 13.6 | 5.4 | 63.3 |
| | | S. D. | ±0.3 | ±0.17 | ±1.4 | ±0.9 | ±1.6 | ±1.2 | ±2.3 |
| | 12.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Mean | 6.5 | 2.00 | 12.1 | 4.1 | 12.2 | 5.0 | 66.5 |
| | | S. D. | ±0.5 | ±0.19 | ±1.0 | ±0.4 | ±1.2 | ±1.2 | ±2.1 |

*: P<0.05, **: P<0.01 (significantly different from control).

Table 10 - continued
Biochemical findings
Male, Female, 52w

| Sex | Group and dose | | T. Bilirubin (mg/dL) | AST (IU/L) | ALT (IU/L) | ALP (IU/L) | T. Cholesterol (mg/dL) | Triglycerides (mg/dL) | Phospholipids (mg/dL) | Glucose (mg/dL) | |
|--------|----------------|------|-------------------------|---------------|---------------|---------------|---------------------------|--------------------------|--------------------------|--------------------|----|
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | | Mean | 0.0 | 85 | 32 | 141 | 80 | 92 | 134 | 125 | |
| | | S.D. | ±0.0 | ±17 | ±15 | ±42 | ±11 | ±41 | ±12 | ±27 | |
| | 0.1 mg/kg | N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | | Mean | 0.0 | 91 | 31 | 165 | 78 | 69 | 123 | 115 | |
| | | S.D. | ±0.0 | ±18 | ±8 | ±56 | ±22 | ±28 | ±26 | ±11 | |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.0 | 89 | 42 | 364** | 82 | 98 | 152 | 139 | |
| | | S.D. | ±0.0 | ±23 | ±31 | ±87 | ±21 | ±32 | ±33 | ±17 | |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 0.0 | 77 | 36 | 565** | 75 | 77 | 143 | 125 | |
| | | S.D. | ±0.0 | ±15 | ±11 | ±137 | ±13 | ±32 | ±15 | ±16 | |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | | Mean | 0.1 | 112 | 37 | 57 | 100 | 95 | 196 | 103 | |
| | | S.D. | ±0.1 | ±98 | ±36 | ±26 | ±23 | ±71 | ±41 | ±9 | |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | | Mean | 0.0 | 92 | 27 | 59 | 104 | 92 | 207 | 110 | |
| | | S.D. | ±0.0 | ±48 | ±12 | ±16 | ±13 | ±51 | ±17 | ±9 | |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
| | | Mean | 0.0 | 132 | 76 | 57 | 108 | 91 | 208 | 106 | |
| | | S.D. | ±0.0 | ±103 | ±103 | ±14 | ±22 | ±61 | ±36 | ±16 | |
| | 12.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | |
| | | Mean | 0.0* | 69 | 25 | 86** | 99 | 77 | 196 | 119* | |
| | | S.D. | ±0.0 | ±13 | ±8 | ±20 | ±21 | ±26 | ±31 | ±16 | |

*: P<0.05, **: P<0.01 (significantly different from control).

Table 10 - continued
Biochemical findings
Male, Female, 52w

| Sex | Group and dose | | BUN | Creatinine | IP | Ca | Na | K | Cl |
|--------|----------------|-------|---------|------------|---------|---------|---------|---------|---------|
| | | | (mg/dL) | (mg/dL) | (mg/dL) | (mg/dL) | (mEq/L) | (mEq/L) | (mEq/L) |
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 9.1 | 0.5 | 5.2 | 10.0 | 147.4 | 4.40 | 107.7 |
| | | S. D. | ±1.5 | ±0.1 | ±0.6 | ±0.2 | ±1.3 | ±0.20 | ±1.1 |
| | 0.1 mg/kg | N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | | Mean | 8.8 | 0.4 | 5.2 | 10.0 | 147.3 | 4.54 | 108.0 |
| | | S. D. | ±0.9 | ±0.1 | ±0.5 | ±0.3 | ±0.9 | ±0.16 | ±2.1 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 10.4 | 0.4 | 5.8* | 10.2 | 146.5 | 4.64 | 107.6 |
| | | S. D. | ±1.9 | ±0.0 | ±0.5 | ±0.5 | ±0.8 | ±0.32 | ±1.8 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 12.8** | 0.4 | 5.6 | 9.9 | 146.2 | 4.63 | 107.1 |
| | | S. D. | ±1.5 | ±0.1 | ±0.6 | ±0.3 | ±1.3 | ±0.26 | ±1.7 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 13.4 | 0.5 | 4.7 | 10.6 | 145.8 | 4.04 | 107.2 |
| | | S. D. | ±2.7 | ±0.1 | ±1.0 | ±0.4 | ±1.2 | ±0.27 | ±1.6 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 12.6 | 0.5 | 4.6 | 10.9 | 146.4 | 3.80 | 107.0 |
| | | S. D. | ±2.8 | ±0.0 | ±0.7 | ±0.3 | ±1.1 | ±0.33 | ±2.5 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 12.7 | 0.5 | 4.6 | 10.6 | 146.0 | 4.19 | 107.4 |
| | | S. D. | ±3.1 | ±0.1 | ±0.6 | ±0.3 | ±1.5 | ±0.32 | ±1.8 |
| | 12.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Mean | 12.1 | 0.4 | 5.0 | 10.5 | 145.7 | 3.96 | 107.9 |
| | | S. D. | ±2.0 | ±0.1 | ±0.8 | ±0.4 | ±1.1 | ±0.21 | ±1.9 |

*: P<0.05, **: P<0.01 (significantly different from control).

Table 11 Necropsy findings
Male, Female, 13w

| Organs and findings | Sex | Male | | | | Female | | | |
|---------------------------|-------------------|---------|-----------|-----------|-----------|---------|-----------|-----------|------------|
| | Group and dose | Control | 0.1 mg/kg | 0.5 mg/kg | 2.5 mg/kg | Control | 0.5 mg/kg | 2.5 mg/kg | 12.5 mg/kg |
| | Number of animals | 10 | 10 | 10 | 9 | 10 | 10 | 10 | 10 |
| Digestive system | | | | | | | | | |
| Liver | | | | | | | | | |
| Enlargement | | 0 | 0 | 0 | 5* | 0 | 0 | 0 | 1 |
| Hematopoietic system | | | | | | | | | |
| Thymus | | | | | | | | | |
| Coloration, dark red | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Urinary system | | | | | | | | | |
| Kidney | | | | | | | | | |
| Pit | | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dilatation, pelvic cavity | | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Mass, light gray | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Integumentary system | | | | | | | | | |
| Integument | | | | | | | | | |
| Loss, hair | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |

*: $P < 0.05$ (significantly different from control).
 No appreciable changes in all other organs and tissues.
 One male in the 2.5 mg/kg group died.

Table 12 Necropsy findings
Male, Female, 52w

| Organs and findings | Sex Group and dose Number of animals | Male | | | | Female | | | |
|---------------------------|--|---------|-----------|-----------|-----------|---------|-----------|-----------|------------|
| | | Control | 0.1 mg/kg | 0.5 mg/kg | 2.5 mg/kg | Control | 0.5 mg/kg | 2.5 mg/kg | 12.5 mg/kg |
| | | 10 | 8 | 10 | 10 | 10 | 10 | 10 | 9 |
| Digestive system | | | | | | | | | |
| Liver | | | | | | | | | |
| Macule, light gray | | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 |
| Macule, dark red | | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |
| Discoloration | | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Enlargement | | 0 | 0 | 7** | 9** | 0 | 0 | 0 | 5* |
| Hernia, diaphragmatic | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Respiratory system | | | | | | | | | |
| Lung | | | | | | | | | |
| Spot, white | | 1 | 0 | 0 | 4 | 1 | 0 | 0 | 0 |
| Coloration, dark red | | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Hematopoietic system | | | | | | | | | |
| Thymus | | | | | | | | | |
| Small | | 10 | 8 | 10 | 9 | 8 | 8 | 10 | 9 |
| Popliteal lymph node | | | | | | | | | |
| Enlargement | | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Spleen | | | | | | | | | |
| Macule, light gray | | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cardiovascular system | | | | | | | | | |
| Heart | | | | | | | | | |
| Coloration, light gray | | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Urinary system | | | | | | | | | |
| Kidney | | | | | | | | | |
| Pit | | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Genital system | | | | | | | | | |
| Testis | | | | | | | | | |
| Small | | 0 | 0 | 0 | 1 | NA | NA | NA | NA |
| Epididymis | | | | | | | | | |
| Small | | 0 | 0 | 0 | 1 | NA | NA | NA | NA |
| Prostate | | | | | | | | | |
| Spot, dark red | | 0 | 0 | 0 | 1 | NA | NA | NA | NA |
| Ovary | | | | | | | | | |
| Enlargement | | NA | NA | NA | NA | 0 | 0 | 2 | 0 |
| Dilatation, ovarian bursa | | | | | | 0 | 0 | 0 | 1 |
| Cyst | | | | | | 2 | 3 | 1 | 2 |

*: P<0.05, **: P<0.01 (significantly different from control).

NA: not applicable.

No appreciable changes in all other organs and tissues.

Two males in the 0.1 mg/kg group and one female in the 12.5 mg/kg group died.

Table 12 - continued

Necropsy findings
Male, Female, 52w

| Organs and findings | Sex Group and dose Number of animals | Male | | | | Female | | | |
|----------------------------|--|---------|-----------|-----------|-----------|---------|-----------|-----------|------------|
| | | Control | 0.1 mg/kg | 0.5 mg/kg | 2.5 mg/kg | Control | 0.5 mg/kg | 2.5 mg/kg | 12.5 mg/kg |
| | | 10 | 8 | 10 | 10 | 10 | 10 | 10 | 9 |
| Genital system | | | | | | | | | |
| Uterus | | NA | NA | NA | NA | | | | |
| Polyp, endometrium | | | | | | 0 | 0 | 0 | 1 |
| Mammary gland | | | | | | | | | |
| Retention, milk | | 0 | 0 | 0 | 0 | 2 | 2 | 3 | 3 |
| Endocrine system | | | | | | | | | |
| Pituitary | | | | | | | | | |
| Spot, dark red | | 0 | 0 | 0 | 0 | 2 | 1 | 3 | 1 |
| Enlargement | | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 1 |
| Nodule, light gray | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Thyroid | | | | | | | | | |
| Defect, left | | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Enlargement, right | | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Adrenal | | | | | | | | | |
| Spot, brown | | 0 | 0 | 0 | 0 | 1 | 2 | 1 | 1 |
| Enlargement | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Integumentary system | | | | | | | | | |
| Integument | | | | | | | | | |
| Nodule, cutis, white | | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Nodule, subcutis, white | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Mass, subcutis, light gray | | 0 | 0 | 0 | 0 | 3 | 0 | 1 | 3 |
| Others | | | | | | | | | |
| Extremity | | | | | | | | | |
| Swelling, hindlimb | | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Corn, hindlimb | | 5 | 5 | 7 | 1 | 1 | 0 | 2 | 2 |

Not significantly different from control.

NA: not applicable.

No appreciable changes in all other organs and tissues.

Two males in the 0.1 mg/kg group and one female in the 12.5 mg/kg group died.

Table 13 Organ weights
Male, Female, 13w

| Sex | Group and dose | | Final body weight | Brain | | Pituitary | | Thyroids | | Heart | |
|--------|----------------|------|-------------------|-------|--------|---------------|------|----------------|------|----------------|--------|
| | | | | (g) | (g) | (g/100 gB.W.) | (mg) | (mg/100 gB.W.) | (mg) | (mg/100 gB.W.) | (g) |
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 530.1 | 2.22 | 0.42 | 14.0 | 2.7 | 20.4 | 3.8 | 1.54 | 0.29 |
| | | S.D. | ±32.1 | ±0.08 | ±0.02 | ±1.6 | ±0.3 | ±5.8 | ±1.0 | ±0.19 | ±0.03 |
| | 0.1 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 566.3 | 2.28 | 0.40 | 13.9 | 2.5 | 26.6* | 4.7 | 1.61 | 0.29 |
| | | S.D. | ±42.2 | ±0.05 | ±0.03 | ±1.3 | ±0.2 | ±5.2 | ±0.8 | ±0.13 | ±0.02 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 546.5 | 2.29 | 0.42 | 14.2 | 2.6 | 24.5 | 4.5 | 1.63 | 0.30 |
| | | S.D. | ±40.3 | ±0.07 | ±0.03 | ±1.2 | ±0.2 | ±5.7 | ±1.1 | ±0.10 | ±0.02 |
| | 2.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Mean | 450.1** | 2.19 | 0.49** | 12.8 | 2.8 | 18.7 | 4.1 | 1.49 | 0.33** |
| | | S.D. | ±27.8 | ±0.07 | ±0.03 | ±0.5 | ±0.2 | ±4.1 | ±0.7 | ±0.09 | ±0.02 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 304.1 | 2.05 | 0.68 | 16.9 | 5.6 | 16.7 | 5.5 | 0.96 | 0.32 |
| | | S.D. | ±26.9 | ±0.06 | ±0.06 | ±1.7 | ±0.5 | ±4.1 | ±1.1 | ±0.07 | ±0.02 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 303.0 | 2.06 | 0.69 | 18.4 | 6.1 | 17.7 | 5.9 | 0.91 | 0.30 |
| | | S.D. | ±31.0 | ±0.09 | ±0.05 | ±1.9 | ±0.7 | ±2.2 | ±0.8 | ±0.08 | ±0.02 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 297.0 | 2.09 | 0.70 | 19.1 | 6.4* | 19.2 | 6.5* | 0.95 | 0.32 |
| | | S.D. | ±17.5 | ±0.08 | ±0.03 | ±2.5 | ±1.0 | ±2.7 | ±1.1 | ±0.06 | ±0.02 |
| | 12.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 299.8 | 2.09 | 0.70 | 18.6 | 6.2 | 18.7 | 6.2 | 0.94 | 0.32 |
| | | S.D. | ±23.1 | ±0.07 | ±0.05 | ±2.9 | ±0.8 | ±2.4 | ±0.7 | ±0.07 | ±0.03 |

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*: P<0.05, **: P<0.01 (significantly different from control).
One male in the 2.5 mg/kg group died.

Table 13 - continued

Organ weights
Male, Female, 13w

| Sex | Group and dose | | Lungs | | Thymus | | Liver | | Spleen | |
|------------|----------------|------|-------|---------------|--------|---------------|---------|---------------|--------|---------------|
| | | | (g) | (g/100 gB.W.) | (g) | (g/100 gB.W.) | (g) | (g/100 gB.W.) | (g) | (g/100 gB.W.) |
| 66 Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.54 | 0.29 | 0.28 | 0.06 | 14.56 | 2.75 | 0.77 | 0.14 |
| | | S.D. | ±0.11 | ±0.02 | ±0.05 | ±0.01 | ±0.81 | ±0.10 | ±0.12 | ±0.02 |
| | 0.1 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.59 | 0.28 | 0.31 | 0.05 | 15.96 | 2.82 | 0.84 | 0.15 |
| | | S.D. | ±0.13 | ±0.03 | ±0.08 | ±0.02 | ±2.02 | ±0.23 | ±0.10 | ±0.01 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.62 | 0.30 | 0.26 | 0.05 | 20.25** | 3.71** | 0.76 | 0.14 |
| | | S.D. | ±0.11 | ±0.02 | ±0.07 | ±0.02 | ±2.00 | ±0.21 | ±0.06 | ±0.01 |
| | 2.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Mean | 1.41 | 0.31 | 0.25 | 0.05 | 23.16** | 5.12** | 0.68 | 0.15 |
| | | S.D. | ±0.09 | ±0.03 | ±0.05 | ±0.01 | ±4.45 | ±0.72 | ±0.07 | ±0.01 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.11 | 0.37 | 0.25 | 0.08 | 7.97 | 2.63 | 0.54 | 0.18 |
| | | S.D. | ±0.09 | ±0.03 | ±0.04 | ±0.01 | ±0.70 | ±0.14 | ±0.06 | ±0.02 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.12 | 0.37 | 0.28 | 0.09 | 7.97 | 2.63 | 0.45** | 0.15** |
| | | S.D. | ±0.09 | ±0.02 | ±0.07 | ±0.02 | ±0.94 | ±0.18 | ±0.06 | ±0.01 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.08 | 0.36 | 0.27 | 0.09 | 8.32 | 2.80 | 0.50 | 0.17 |
| | | S.D. | ±0.06 | ±0.02 | ±0.04 | ±0.01 | ±0.52 | ±0.18 | ±0.07 | ±0.02 |
| | 12.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.14 | 0.38 | 0.27 | 0.09 | 11.63** | 3.88** | 0.49 | 0.17 |
| | | S.D. | ±0.11 | ±0.03 | ±0.06 | ±0.02 | ±1.72 | ±0.50 | ±0.05 | ±0.01 |

** : P<0.01 (significantly different from control).
One male in the 2.5 mg/kg group died.

Table 13 - continued

Organ weights
Male, Female, 13w

| Sex | Group and dose | | Kidneys | | Adrenals | | Epididymides | | Testes | |
|--------|----------------|-------|---------|----------------|----------|-----------------|--------------|----------------|--------|----------------|
| | | | (g) | (g/100 gB. W.) | (mg) | (mg/100 gB. W.) | (g) | (g/100 gB. W.) | (g) | (g/100 gB. W.) |
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 3.30 | 0.62 | 57.1 | 10.8 | 1.39 | 0.26 | 3.46 | 0.65 |
| | | S. D. | ±0.28 | ±0.04 | ±7.0 | ±1.5 | ±0.14 | ±0.02 | ±0.28 | ±0.07 |
| | 0.1 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 3.49 | 0.62 | 61.0 | 10.8 | 1.39 | 0.25 | 3.47 | 0.62 |
| | | S. D. | ±0.29 | ±0.02 | ±6.1 | ±1.0 | ±0.15 | ±0.02 | ±0.23 | ±0.07 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 3.64 | 0.67 | 58.0 | 10.7 | 1.24* | 0.23* | 3.31 | 0.61 |
| | | S. D. | ±0.29 | ±0.06 | ±3.9 | ±0.8 | ±0.08 | ±0.02 | ±0.39 | ±0.06 |
| | 2.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Mean | 3.16 | 0.70* | 50.5* | 11.2 | 1.27 | 0.28 | 3.65 | 0.81** |
| | | S. D. | ±0.45 | ±0.07 | ±5.3 | ±1.1 | ±0.11 | ±0.03 | ±0.15 | ±0.07 |
| Female | Control | N | 10 | 10 | 10 | 10 | | | | |
| | | Mean | 2.12 | 0.70 | 66.0 | 21.8 | | | | |
| | | S. D. | ±0.72 | ±0.25 | ±7.8 | ±2.6 | | | | |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | | | | |
| | | Mean | 1.93 | 0.64 | 66.5 | 22.1 | | | | |
| | | S. D. | ±0.29 | ±0.07 | ±6.4 | ±2.4 | | | | |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | | | | |
| | | Mean | 1.89 | 0.64 | 64.7 | 21.8 | | | | |
| | | S. D. | ±0.11 | ±0.05 | ±6.1 | ±2.5 | | | | |
| | 12.5 mg/kg | N | 10 | 10 | 10 | 10 | | | | |
| | | Mean | 1.96 | 0.66 | 61.8 | 20.6 | | | | |
| | | S. D. | ±0.15 | ±0.06 | ±6.7 | ±1.6 | | | | |

*, P<0.05, **: P<0.01 (significantly different from control).
One male in the 2.5 mg/kg group died.

Table 13 - continued
Organ weights
Male, Female, 13w

| Sex | Group and dose | | Ovaries | | Uterus | |
|-----------|----------------|-------|---------|-----------------|--------|----------------|
| | | | (mg) | (mg/100 gB. W.) | (g) | (g/100 gB. W.) |
| Male | Control | N | | | | |
| | | Mean | | | | |
| | | S. D. | | | | |
| | 0.1 mg/kg | N | | | | |
| Mean | | | | | | |
| S. D. | | | | | | |
| 0.5 mg/kg | N | | | | | |
| | Mean | | | | | |
| | S. D. | | | | | |
| 2.5 mg/kg | N | | | | | |
| | Mean | | | | | |
| | S. D. | | | | | |
| Female | Control | N | 10 | 10 | 10 | 10 |
| | | Mean | 78.5 | 26.1 | 0.58 | 0.19 |
| | | S. D. | ±7.8 | ±4.0 | ±0.09 | ±0.03 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 |
| | | Mean | 79.8 | 26.5 | 0.65 | 0.22 |
| | | S. D. | ±8.9 | ±3.2 | ±0.08 | ±0.04 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 |
| | | Mean | 79.3 | 26.9 | 0.56 | 0.19 |
| | | S. D. | ±11.9 | ±4.6 | ±0.06 | ±0.03 |
| | 12.5 mg/kg | N | 10 | 10 | 10 | 10 |
| | | Mean | 80.4 | 27.0 | 0.63 | 0.21 |
| | | S. D. | ±10.9 | ±4.0 | ±0.08 | ±0.03 |

Not significantly different from control.

Table 14 Organ weights
Male, Female, 52w

| Sex | Group and dose | | Final body weight | Brain | | Pituitary | | Thyroids | | Heart | |
|--------|----------------|------|-------------------|-------|---------------|-----------|----------------|----------|----------------|-------|---------------|
| | | | (g) | (g) | (g/100 gB.W.) | (mg) | (mg/100 gB.W.) | (mg) | (mg/100 gB.W.) | (g) | (g/100 gB.W.) |
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 819.9 | 2.41 | 0.30 | 15.8 | 2.0 | 31.5 | 3.8 | 1.89 | 0.23 |
| | | S.D. | ±145.4 | ±0.12 | ±0.04 | ±1.8 | ±0.2 | ±11.3 | ±0.9 | ±0.25 | ±0.02 |
| | 0.1 mg/kg | N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | | Mean | 792.5 | 2.41 | 0.31 | 15.7 | 2.0 | 31.4 | 3.9 | 1.93 | 0.25 |
| | | S.D. | ±140.4 | ±0.08 | ±0.07 | ±1.7 | ±0.5 | ±11.9 | ±1.0 | ±0.19 | ±0.04 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 842.4 | 2.41 | 0.29 | 16.2 | 1.9 | 34.0 | 4.1 | 2.05 | 0.25 |
| | | S.D. | ±136.1 | ±0.07 | ±0.04 | ±1.3 | ±0.3 | ±6.0 | ±0.8 | ±0.17 | ±0.03 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 614.2** | 2.36 | 0.39** | 16.8 | 2.8** | 29.7 | 4.9* | 1.87 | 0.31** |
| | | S.D. | ±97.3 | ±0.10 | ±0.05 | ±3.1 | ±0.3 | ±5.7 | ±0.9 | ±0.27 | ±0.03 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 423.2 | 2.17 | 0.54 | 27.9 | 6.6 | 24.0 | 5.7 | 1.15 | 0.28 |
| | | S.D. | ±87.2 | ±0.08 | ±0.12 | ±11.9 | ±2.3 | ±5.8 | ±1.1 | ±0.16 | ±0.04 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 441.8 | 2.20 | 0.51 | 30.9 | 7.0 | 24.6 | 5.5 | 1.23 | 0.28 |
| | | S.D. | ±71.4 | ±0.09 | ±0.07 | ±16.5 | ±3.8 | ±8.7 | ±1.3 | ±0.16 | ±0.04 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 481.0 | 2.16 | 0.47 | 32.8 | 7.1 | 27.6 | 5.9 | 1.23 | 0.26 |
| | | S.D. | ±104.7 | ±0.06 | ±0.10 | ±13.6 | ±3.2 | ±4.7 | ±1.1 | ±0.17 | ±0.04 |
| | 12.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Mean | 425.8 | 2.17 | 0.52 | 30.5 | 7.4 | 26.5 | 6.4 | 1.24 | 0.29 |
| | | S.D. | ±71.4 | ±0.07 | ±0.08 | ±9.9 | ±2.4 | ±4.1 | ±1.4 | ±0.09 | ±0.03 |

#: P<0.05, **: P<0.01 (significantly different from control).
Two males in the 0.1 mg/kg group and one female in the 12.5 mg/kg group died.

Table 14 - continued
Organ weights
Male, Female, 52w

| Sex | Group and dose | | Lungs | | Thymus | | Liver | | Spleen | |
|--------|----------------|------|-------|---------------|--------|---------------|---------|---------------|--------|---------------|
| | | | (g) | (g/100 gB.W.) | (g) | (g/100 gB.W.) | (g) | (g/100 gB.W.) | (g) | (g/100 gB.W.) |
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.88 | 0.23 | 0.08 | 0.01 | 18.35 | 2.22 | 0.99 | 0.12 |
| | | S.D. | ±0.16 | ±0.02 | ±0.02 | ±0.00 | ±4.61 | ±0.25 | ±0.24 | ±0.02 |
| | 0.1 mg/kg | N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | | Mean | 1.86 | 0.24 | 0.08 | 0.01 | 17.79 | 2.26 | 0.96 | 0.13 |
| | | S.D. | ±0.05 | ±0.05 | ±0.03 | ±0.00 | ±2.65 | ±0.20 | ±0.07 | ±0.03 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.88 | 0.23 | 0.07 | 0.01 | 24.85** | 2.95** | 1.06 | 0.13 |
| | | S.D. | ±0.22 | ±0.02 | ±0.02 | ±0.00 | ±5.23 | ±0.47 | ±0.15 | ±0.03 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.79 | 0.29** | 0.09 | 0.01 | 25.09** | 4.13** | 0.89 | 0.15 |
| | | S.D. | ±0.16 | ±0.03 | ±0.02 | ±0.00 | ±3.69 | ±0.62 | ±0.19 | ±0.02 |
| Female | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.34 | 0.33 | 0.09 | 0.02 | 10.55 | 2.48 | 0.62 | 0.15 |
| | | S.D. | ±0.17 | ±0.07 | ±0.03 | ±0.01 | ±3.14 | ±0.39 | ±0.15 | ±0.02 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.29 | 0.30 | 0.10 | 0.02 | 10.70 | 2.42 | 0.60 | 0.14 |
| | | S.D. | ±0.12 | ±0.05 | ±0.03 | ±0.01 | ±2.03 | ±0.14 | ±0.09 | ±0.02 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 1.35 | 0.29 | 0.10 | 0.02 | 11.66 | 2.45 | 0.62 | 0.13 |
| | | S.D. | ±0.12 | ±0.07 | ±0.02 | ±0.00 | ±2.41 | ±0.32 | ±0.10 | ±0.03 |
| | 12.5 mg/kg | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Mean | 1.33 | 0.32 | 0.09 | 0.02 | 15.04** | 3.54** | 0.60 | 0.14 |
| | | S.D. | ±0.08 | ±0.05 | ±0.02 | ±0.01 | ±2.96 | ±0.41 | ±0.06 | ±0.02 |

** : P<0.01 (significantly different from control).

Two males in the 0.1 mg/kg group and one female in the 12.5 mg/kg group died.

Table 14 - continued
Organ weights
Male, Female, 52w

| Sex | Group and dose | | Kidneys | | Adrenals | | Epididymides | | Testes | |
|--------|----------------|------|---------|---------------|----------|----------------|--------------|---------------|--------|---------------|
| | | | (g) | (g/100 gB.W.) | (mg) | (mg/100 gB.W.) | (g) | (g/100 gB.W.) | (g) | (g/100 gB.W.) |
| Male | Control | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 3.78 | 0.47 | 63.7 | 7.9 | 1.30 | 0.16 | 3.60 | 0.45 |
| | | S.D. | ±0.50 | ±0.05 | ±8.7 | ±1.2 | ±0.10 | ±0.03 | ±0.33 | ±0.06 |
| | 0.1 mg/kg | N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | | Mean | 3.76 | 0.48 | 61.6 | 8.0 | 1.35 | 0.18 | 3.61 | 0.47 |
| | | S.D. | ±0.46 | ±0.08 | ±8.3 | ±1.9 | ±0.08 | ±0.04 | ±0.36 | ±0.10 |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 4.29 | 0.51 | 60.9 | 7.3 | 1.37 | 0.17 | 3.78 | 0.46 |
| | | S.D. | ±0.63 | ±0.06 | ±10.9 | ±1.1 | ±0.13 | ±0.02 | ±0.31 | ±0.07 |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | | Mean | 4.12 | 0.68** | 55.6 | 9.1 | 1.28 | 0.22* | 3.65 | 0.61** |
| | | S.D. | ±0.40 | ±0.09 | ±8.8 | ±0.9 | ±0.26 | ±0.06 | ±0.73 | ±0.15 |
| Female | Control | N | 10 | 10 | 10 | 10 | | | | |
| | | Mean | 2.29 | 0.55 | 76.3 | 18.4 | | | | |
| | | S.D. | ±0.43 | ±0.08 | ±16.8 | ±4.0 | | | | |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 | | | | |
| | | Mean | 2.35 | 0.54 | 79.6 | 18.0 | | | | |
| | | S.D. | ±0.33 | ±0.06 | ±25.3 | ±4.7 | | | | |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 | | | | |
| | | Mean | 2.39 | 0.52 | 81.2 | 17.6 | | | | |
| | | S.D. | ±0.29 | ±0.13 | ±32.9 | ±8.1 | | | | |
| | 12.5 mg/kg | N | 9 | 9 | 9 | 9 | | | | |
| | | Mean | 2.63 | 0.63 | 73.9 | 17.7 | | | | |
| | | S.D. | ±0.26 | ±0.09 | ±10.2 | ±3.4 | | | | |

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*: P<0.05, **: P<0.01 (significantly different from control).
Two males in the 0.1 mg/kg group and one female in the 12.5 mg/kg group died.

Table 14 - continued Organ weights
Male, Female, 52w

| Sex | Group and dose | | Ovaries | | Uterus | |
|--------|----------------|------|---------|----------------|--------|---------------|
| | | | (mg) | (mg/100 gB.W.) | (g) | (g/100 gB.W.) |
| Male | Control | N | | | | |
| | | Mean | | | | |
| | | S.D. | | | | |
| | | | | | | |
| | 0.1 mg/kg | N | | | | |
| | | Mean | | | | |
| | | S.D. | | | | |
| | | | | | | |
| | 0.5 mg/kg | N | | | | |
| | | Mean | | | | |
| | | S.D. | | | | |
| | | | | | | |
| | 2.5 mg/kg | N | | | | |
| | | Mean | | | | |
| | | S.D. | | | | |
| | | | | | | |
| Female | Control | N | 10 | 10 | 10 | 10 |
| | | Mean | 67.0 | 16.0 | 0.97 | 0.24 |
| | | S.D. | ±17.0 | ±3.3 | ±0.25 | ±0.08 |
| | | | | | | |
| | 0.5 mg/kg | N | 10 | 10 | 10 | 10 |
| | | Mean | 62.2 | 14.3 | 0.96 | 0.22 |
| | | S.D. | ±17.5 | ±4.4 | ±0.24 | ±0.06 |
| | | | | | | |
| | 2.5 mg/kg | N | 10 | 10 | 10 | 10 |
| | | Mean | 64.5 | 13.5 | 0.97 | 0.22 |
| | | S.D. | ±32.6 | ±5.5 | ±0.26 | ±0.09 |
| | | | | | | |
| | 12.5 mg/kg | N | 8 | 8 | 9 | 9 |
| | | Mean | 60.9 | 14.3 | 1.03 | 0.25 |
| | | S.D. | ±18.2 | ±2.5 | ±0.22 | ±0.08 |
| | | | | | | |

Not significantly different from control.

One female in the 12.5 mg/kg group died.

The ovaries in one female in the 12.5 mg/kg group were not weighed due to the dilatation of paraovarian bursa, prevents obtaining the actual ovary weights.

Table 15 Histopathological findings
Male, Female, 13w

| Organs and findings | Sex | | Male | | | | | | | | | | | | | | | | | | |
|---|-------------------|---------|---------|-----|-------|------|-----------|----|-----|-------|-----------|----|----|--------|-----------|---|---|----|-----|-------|-----|
| | Group and dose | | Control | | | | 0.1 mg/kg | | | | 0.5 mg/kg | | | | 2.5 mg/kg | | | | | | |
| | Number of animals | | 10 | | | | 10 | | | | 10 | | | | 9 | | | | | | |
| | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | |
| Digestive system | | | | | | | | | | | | | | | | | | | | | |
| Tongue | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | | |
| Esophagus | | (10) | | | | (0) | | | | (0) | | | | (9) | | | | | | | |
| Fibrosis, muscular layer | | 9 | 1 | 0 | 0 | 1 | | | | | 9 | 0 | 0 | 0 | 0 | | | | | | |
| Stomach | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | | |
| Duodenum | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | | |
| Jejunum | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | | |
| Ileum | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | | |
| Cecum | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | | |
| Colon | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | | |
| Rectum | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | | |
| Submaxillary gland | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | | |
| Sublingual gland | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | | |
| Parotid gland | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | | |
| Liver | | (10) | | | | (10) | | | | (10) | | | | (9) | | | | | | | |
| Degeneration, hepatocyte, fatty, midzonal | | 10 | 0 | 0 | 0 | 0 | 9 | 1 | 0 | 0 | 1 | 10 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 0 |
| Degeneration, hepatocyte, fatty, periportal | | 10 | 0 | 0 | 0 | 0 | 10 | 0 | 0 | 0 | 0 | 10 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 0 |
| Necrosis, hepatocyte, focal | | 9 | 1 | 0 | 0 | 1 | 10 | 0 | 0 | 0 | 0 | 9 | 1 | 0 | 0 | 1 | 7 | 2 | 0 | 0 | 2 |
| Hypertrophy, hepatocyte ¹⁾ , centrilobular | | 10 | 0 | 0 | 0 | 0 | 10 | 0 | 0 | 0 | 0 | 7 | 3 | 0 | 0 | 3 | 0 | 6 | 3 | 0 | 9** |
| Cellular infiltration, mononuclear cell | | 9 | 1 | 0 | 0 | 1 | 7 | 3 | 0 | 0 | 3 | 8 | 2 | 0 | 0 | 2 | 9 | 0 | 0 | 0 | 0 |
| Pancreas | | (10) | | | | (0) | | | | (0) | | | | (9) | | | | | | | |
| Atrophy, acinus, focal | | 10 | 0 | 0 | 0 | 0 | | | | | 9 | 0 | 0 | 0 | 0 | | | | | | |
| Respiratory system | | | | | | | | | | | | | | | | | | | | | |
| Trachea | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | | |
| Lung | | (10) | | | | (0) | | | | (0) | | | | (9) | | | | | | | |
| Accumulation, foam cell, alveolus | | 9 | 1 | 0 | 0 | 1 | | | | | 6 | 3 | 0 | 0 | 3 | | | | | | |
| Mineralization, artery | | 9 | 1 | 0 | 0 | 1 | | | | | 8 | 1 | 0 | 0 | 1 | | | | | | |
| Hematopoietic system | | | | | | | | | | | | | | | | | | | | | |
| Thymus | | (10) | | | | (0) | | | | (0) | | | | (9) | | | | | | | |
| Hemorrhage | | 10 | 0 | 0 | 0 | 0 | | | | | 9 | 0 | 0 | 0 | 0 | | | | | | |
| Submaxillary lymph node | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | | |
| Mesenteric lymph node | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | | |

** : P < 0.01 (significantly different from control).
Grade sign: -, none; +, mild; ++, moderate; +++, marked.
NR: no remarkable changes.

1) with eosinophilic granular cytoplasm.

Figures in parentheses are number of animals with tissues examined histopathologically.
One male in the 2.5 mg/kg group died.

Table 15 - continued
Histopathological findings
Male, Female, 13w

| Organs and findings | Sex | Group and dose | Male | | | | | | | | | | | | | | | | | | | |
|---|-----|----------------|---------|---|----|-----|-------|-----------|---|----|-----|-------|-----------|---|----|-----|-------|-----------|---|----|-----|-------|
| | | | Control | | | | | 0.1 mg/kg | | | | | 0.5 mg/kg | | | | | 2.5 mg/kg | | | | |
| | | | 10 | | | | | 10 | | | | | 10 | | | | | 9 | | | | |
| | | | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total |
| Hematopoietic system | | | | | | | | | | | | | | | | | | | | | | |
| Spleen | | | | | | | | | | | | | | | | | | | | | | |
| NR (10) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| NR (9) | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow (sternum) | | | | | | | | | | | | | | | | | | | | | | |
| NR (10) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| NR (9) | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow (femur) | | | | | | | | | | | | | | | | | | | | | | |
| NR (10) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| NR (9) | | | | | | | | | | | | | | | | | | | | | | |
| Cardiovascular system | | | | | | | | | | | | | | | | | | | | | | |
| Heart | | | | | | | | | | | | | | | | | | | | | | |
| (10) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, mononuclear cell | | | | | | | | | | | | | | | | | | | | | | |
| 8 2 0 0 2 | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| Aorta | | | | | | | | | | | | | | | | | | | | | | |
| NR (10) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| 5 4 0 0 4 | | | | | | | | | | | | | | | | | | | | | | |
| NR (9) | | | | | | | | | | | | | | | | | | | | | | |
| Urinary system | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | | | | | | | | | | | | | | | | | | | | | | |
| (10) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| 8 1 0 0 1 | | | | | | | | | | | | | | | | | | | | | | |
| 8 1 0 0 1 | | | | | | | | | | | | | | | | | | | | | | |
| 9 0 0 0 0 | | | | | | | | | | | | | | | | | | | | | | |
| 9 0 0 0 0 | | | | | | | | | | | | | | | | | | | | | | |
| 9 0 0 0 0 | | | | | | | | | | | | | | | | | | | | | | |
| 9 0 0 0 0 | | | | | | | | | | | | | | | | | | | | | | |
| 9 0 0 0 0 | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | | | | | | | | | | | | | | | | | | | | | | |
| NR (10) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| NR (9) | | | | | | | | | | | | | | | | | | | | | | |
| Genital system | | | | | | | | | | | | | | | | | | | | | | |
| Testis | | | | | | | | | | | | | | | | | | | | | | |
| NR (10) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| NR (9) | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | | | | | | | | | | | | | | | | | | | | | | |
| NR (10) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| NR (9) | | | | | | | | | | | | | | | | | | | | | | |
| Prostate | | | | | | | | | | | | | | | | | | | | | | |
| (10) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, mononuclear cell | | | | | | | | | | | | | | | | | | | | | | |
| 8 2 0 0 2 | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| 7 2 0 0 2 | | | | | | | | | | | | | | | | | | | | | | |
| NR (9) | | | | | | | | | | | | | | | | | | | | | | |
| Seminal vesicle | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| Ovary | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| Vagina | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | | | | | | | | | | | | | | | | | | | | | | |
| NR (10) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| NR (9) | | | | | | | | | | | | | | | | | | | | | | |
| Endocrine system | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | | | | | | | | | | | | | | | | | | | | | | |
| NR (10) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| NR (9) | | | | | | | | | | | | | | | | | | | | | | |
| Thyroid | | | | | | | | | | | | | | | | | | | | | | |
| (10) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | | |
| Remnant, ultimobranchial body | | | | | | | | | | | | | | | | | | | | | | |
| 10 0 0 0 0 | | | | | | | | | | | | | | | | | | | | | | |
| 8 1 0 0 1 | | | | | | | | | | | | | | | | | | | | | | |

Not significantly different from control.

Grade sign: -, none; +, mild(existent of tumor); ++, moderate; +++, marked.

NR: no remarkable changes.

NA: not applicable.

Figures in parentheses are number of animals with tissues examined histopathologically.

One male in the 2.5 mg/kg group died.

Table 15 - continued

Histopathological findings
Male, Female, 13w

| Organs and findings | Sex | Group and dose | Male | | | | | | | | | | | | | | | | | | | |
|-----------------------------------|-----|----------------|---------|----|-----|-------|---|-----------|----|-----|-------|---|-----------|----|-----|-------|---|-----------|----|-----|-------|--|
| | | | Control | | | | | 0.1 mg/kg | | | | | 0.5 mg/kg | | | | | 2.5 mg/kg | | | | |
| | | | 10 | | | | | 10 | | | | | 10 | | | | | 9 | | | | |
| | | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | |
| Endocrine system | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal | | | | | | | | | | | | | | | | | | | | | | |
| Hypertrophy, cortical cell, focal | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | |
| Nervous system | | | | | | | | | | | | | | | | | | | | | | |
| Cerebrum | | | | | | | | | | | | | | | | | | | | | | |
| Dilatation, lateral ventricle | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | |
| Cerebellum | | | | | | | | | | | | | | | | | | | | | | |
| Medulla oblongata | | | | | | | | | | | | | | | | | | | | | | |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | |
| Optic nerve | | | | | | | | | | | | | | | | | | | | | | |
| Sciatic nerve | | | | | | | | | | | | | | | | | | | | | | |
| Special sense organs | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | |
| Musculoskeletal system | | | | | | | | | | | | | | | | | | | | | | |
| M. biceps femoris | | | | | | | | | | | | | | | | | | | | | | |
| Sternum | | | | | | | | | | | | | | | | | | | | | | |
| Femur | | | | | | | | | | | | | | | | | | | | | | |
| Integumentary system | | | | | | | | | | | | | | | | | | | | | | |
| Integument | | | | | | | | | | | | | | | | | | | | | | |

Not significantly different from control.

Grade sign: -, none; +, mild; ++, moderate; +++, marked.

NR: no remarkable changes.

Figures in parentheses are number of animals with tissues examined histopathologically.

One male in the 2.5 mg/kg group died.

Table 15 - continued Histopathological findings
Male, Female, 13w

| Organs and findings | Sex | Group and dose | Female | | | | | | | | | | | | | | | | | | | |
|---|-----|----------------|---------|---|----|-----|-------|-----------|---|----|-----|-------|-----------|---|----|-----|-------|------------|---|-----|-----|-------|
| | | | Control | | | | | 0.5 mg/kg | | | | | 2.5 mg/kg | | | | | 12.5 mg/kg | | | | |
| | | | 10 | | | | | 10 | | | | | 10 | | | | | 10 | | | | |
| | | | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total |
| Digestive system | | | | | | | | | | | | | | | | | | | | | | |
| Tongue | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | | | | | | | | | | | | | | | | | | | | | | |
| Fibrosis, muscular layer | | 10 | 0 | 0 | 0 | 0 | | | | | | | | | | 9 | 1 | 0 | 0 | 1 | | |
| Stomach | | | | | | | | | | | | | | | | | | | | | | |
| Duodenum | | | | | | | | | | | | | | | | | | | | | | |
| Jejunum | | | | | | | | | | | | | | | | | | | | | | |
| Ileum | | | | | | | | | | | | | | | | | | | | | | |
| Cecum | | | | | | | | | | | | | | | | | | | | | | |
| Colon | | | | | | | | | | | | | | | | | | | | | | |
| Rectum | | | | | | | | | | | | | | | | | | | | | | |
| Submaxillary gland | | | | | | | | | | | | | | | | | | | | | | |
| Sublingual gland | | | | | | | | | | | | | | | | | | | | | | |
| Parotid gland | | | | | | | | | | | | | | | | | | | | | | |
| Liver | | | | | | | | | | | | | | | | | | | | | | |
| Degeneration, hepatocyte, fatty, midzonal | | 10 | 0 | 0 | 0 | 0 | | | | | | | | | | 10 | 0 | 0 | 0 | 0 | | |
| Degeneration, hepatocyte, fatty, periportal | | 9 | 1 | 0 | 0 | 1 | | | | | | | | | | 10 | 0 | 0 | 0 | 0 | | |
| Necrosis, hepatocyte, focal | | 10 | 0 | 0 | 0 | 0 | | | | | | | | | | 10 | 0 | 0 | 0 | 0 | | |
| Hypertrophy, hepatocyte ¹⁾ , centrilobular | | 10 | 0 | 0 | 0 | 0 | | | | | | | | | | 4 | 6 | 0 | 0 | 6** | | |
| Cellular infiltration, mononuclear cell | | 7 | 3 | 0 | 0 | 3 | | | | | | | | | | 8 | 2 | 0 | 0 | 2 | | |
| Pancreas | | | | | | | | | | | | | | | | | | | | | | |
| Atrophy, acinus, focal | | 9 | 1 | 0 | 0 | 1 | | | | | | | | | | | | | | | | |
| Respiratory system | | | | | | | | | | | | | | | | | | | | | | |
| Trachea | | | | | | | | | | | | | | | | | | | | | | |
| Lung | | | | | | | | | | | | | | | | | | | | | | |
| Accumulation, foam cell, alveolus | | 9 | 1 | 0 | 0 | 1 | | | | | | | | | | 9 | 1 | 0 | 0 | 1 | | |
| Mineralization, artery | | 9 | 1 | 0 | 0 | 1 | | | | | | | | | | 8 | 2 | 0 | 0 | 2 | | |
| Hematopoietic system | | | | | | | | | | | | | | | | | | | | | | |
| Thymus | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | 9 | 1 | 0 | 0 | 1 | | | | | | | | | | 10 | 0 | 0 | 0 | 0 | | |
| Submaxillary lymph node | | | | | | | | | | | | | | | | | | | | | | |
| Mesenteric lymph node | | | | | | | | | | | | | | | | | | | | | | |

** : P<0.01 (significantly different from control).
Grade sign: -, none; +, mild; ++, moderate; +++, marked.
NR: no remarkable changes.

1) with eosinophilic granular cytoplasm.

Figures in parentheses are number of animals with tissues examined histopathologically.

Table 15 - continued

Histopathological findings
Male, Female, 13w

| Organs and findings | Sex | | Female | | | | | | | | | | | | | | | | | |
|---|-------------------|---------|---------|-----|-------|-----|-----------|----|-----|-------|-----------|---|----|---------|------------|---|---|----|-----|-------|
| | Group and dose | | Control | | | | 0.5 mg/kg | | | | 2.5 mg/kg | | | | 12.5 mg/kg | | | | | |
| | Number of animals | | 10 | | | | 10 | | | | 10 | | | | 10 | | | | | |
| | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total |
| Hematopoietic system | | | | | | | | | | | | | | | | | | | | |
| Spleen | | NR (10) | | | | (0) | | | | (0) | | | | NR (10) | | | | | | |
| Bone marrow (sternum) | | NR (10) | | | | (0) | | | | (0) | | | | NR (10) | | | | | | |
| Bone marrow (femur) | | NR (10) | | | | (0) | | | | (0) | | | | NR (10) | | | | | | |
| Cardiovascular system | | | | | | | | | | | | | | | | | | | | |
| Heart | | (10) | | | | (0) | | | | (0) | | | | (10) | | | | | | |
| Cellular infiltration, mononuclear cell | | 10 | 0 | 0 | 0 | 0 | (0) | | | | (0) | | | | 10 | 0 | 0 | 0 | 0 | |
| Aorta | | NR (10) | | | | (0) | | | | (0) | | | | NR (10) | | | | | | |
| Urinary system | | | | | | | | | | | | | | | | | | | | |
| Kidney | | (10) | | | | (0) | | | | (0) | | | | (10) | | | | | | |
| Tubule, basophilic | | 10 | 0 | 0 | 0 | 0 | (0) | | | | (0) | | | | 10 | 0 | 0 | 0 | 0 | |
| Cast, proteinaceous | | 10 | 0 | 0 | 0 | 0 | (0) | | | | (0) | | | | 10 | 0 | 0 | 0 | 0 | |
| Cellular infiltration, pelvis, neutrophil | | 10 | 0 | 0 | 0 | 0 | (0) | | | | (0) | | | | 10 | 0 | 0 | 0 | 0 | |
| Mineralization, corticomedullary | | 9 | 1 | 0 | 0 | 1 | (0) | | | | (0) | | | | 10 | 0 | 0 | 0 | 0 | |
| Nephroblastoma | | 9 | 1 | 0 | 0 | 1 | (0) | | | | (0) | | | | 10 | 0 | 0 | 0 | 0 | |
| Urinary bladder | | NR (10) | | | | (0) | | | | (0) | | | | NR (10) | | | | | | |
| Genital system | | | | | | | | | | | | | | | | | | | | |
| Testis | | NA | | | | NA | | | | NA | | | | NA | | | | | | |
| Epididymis | | NA | | | | NA | | | | NA | | | | NA | | | | | | |
| Prostate | | NA | | | | NA | | | | NA | | | | NA | | | | | | |
| Cellular infiltration, mononuclear cell | | NA | | | | NA | | | | NA | | | | NA | | | | | | |
| Seminal vesicle | | NA | | | | NA | | | | NA | | | | NA | | | | | | |
| Ovary | | NR (10) | | | | (0) | | | | (0) | | | | NR (10) | | | | | | |
| Uterus | | NR (10) | | | | (0) | | | | (0) | | | | NR (10) | | | | | | |
| Vagina | | NR (10) | | | | (0) | | | | (0) | | | | NR (10) | | | | | | |
| Mammary gland | | NR (10) | | | | (0) | | | | (0) | | | | NR (10) | | | | | | |
| Endocrine system | | | | | | | | | | | | | | | | | | | | |
| Pituitary | | NR (10) | | | | (0) | | | | (0) | | | | NR (10) | | | | | | |
| Thyroid | | (10) | | | | (0) | | | | (0) | | | | (10) | | | | | | |
| Remnant, ultimobranchial body | | 6 | 4 | 0 | 0 | 4 | (0) | | | | (0) | | | | 8 | 2 | 0 | 0 | 2 | |

Not significantly different from control.
Grade sign: -, none; +, mild(existent of tumor); ++, moderate; +++, marked.
NR: no remarkable changes.
NA: not applicable.
Figures in parentheses are number of animals with tissues examined histopathologically.

Table 15 - continued

Histopathological findings
Male, Female, 13w

| Organs and findings | Sex | Group and dose | Female | | | | | | | | | | | | | | | | | | | |
|-----------------------------------|-----|----------------|---------|---|----|-----|-------|-----------|---|----|-----|-------|-----------|---|----|-----|-------|------------|---|----|-----|-------|
| | | | Control | | | | | 0.5 mg/kg | | | | | 2.5 mg/kg | | | | | 12.5 mg/kg | | | | |
| | | | 10 | | | | | 10 | | | | | 10 | | | | | 10 | | | | |
| | | | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total |
| Endocrine system | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal | | | | | | | | | | | | | | | | | | | | | | |
| Hypertrophy, cortical cell, focal | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | |
| Nervous system | | | | | | | | | | | | | | | | | | | | | | |
| Cerebrum | | | | | | | | | | | | | | | | | | | | | | |
| Dilatation, lateral ventricle | | | | | | | | | | | | | | | | | | | | | | |
| Cerebellum | | | | | | | | | | | | | | | | | | | | | | |
| Medulla oblongata | | | | | | | | | | | | | | | | | | | | | | |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | |
| Optic nerve | | | | | | | | | | | | | | | | | | | | | | |
| Sciatic nerve | | | | | | | | | | | | | | | | | | | | | | |
| Special sense organs | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | |
| Musculoskeletal system | | | | | | | | | | | | | | | | | | | | | | |
| M. biceps femoris | | | | | | | | | | | | | | | | | | | | | | |
| Sternum | | | | | | | | | | | | | | | | | | | | | | |
| Femur | | | | | | | | | | | | | | | | | | | | | | |
| Integumentary system | | | | | | | | | | | | | | | | | | | | | | |
| Integument | | | | | | | | | | | | | | | | | | | | | | |

Not significantly different from control.

Grade sign: -, none; +, mild; ++, moderate; +++, marked.

NR: no remarkable changes.

Figures in parentheses are number of animals with tissues examined histopathologically.

Table 16 - continued
Histopathological findings
Male, Female, 52w

| Organs and findings | Sex | Group and dose | Male | | | | | | | | | | | | | | | | | |
|----------------------|-----|----------------|---------|---|----|-----|-----------|---|---|----|-----------|-------|---|---|-----------|-----|-------|---|---|----|
| | | | Control | | | | 0.1 mg/kg | | | | 0.5 mg/kg | | | | 2.5 mg/kg | | | | | |
| | | | 10 | | | | 8 | | | | 10 | | | | 10 | | | | | |
| | | | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ |
| Digestive system | | | | | | | | | | | | | | | | | | | | |
| Pancreas | | | | | | | | | | | | | | | | | | | | |
| | | | (10) | | | | (0) | | | | (0) | | | | (10) | | | | | |
| | | | 10 | 0 | 0 | 0 | 0 | | | | | | | | | 9 | 1 | 0 | 0 | 1 |
| | | | 8 | 2 | 0 | 0 | 2 | | | | | | | | 7 | 3 | 0 | 0 | 3 | |
| | | | 10 | 0 | 0 | 0 | 0 | | | | | | | | 10 | 0 | 0 | 0 | 0 | |
| | | | 9 | 1 | 0 | 0 | 1 | | | | | | | | 10 | 0 | 0 | 0 | 0 | |
| Respiratory system | | | | | | | | | | | | | | | | | | | | |
| Trachea | | | | | | | | | | | | | | | | | | | | |
| | | | (10) | | | | (0) | | | | (0) | | | | (10) | | | | | |
| | | | 10 | 0 | 0 | 0 | 0 | | | | | | | | 10 | 0 | 0 | 0 | 0 | |
| Lung | | | | | | | | | | | | | | | | | | | | |
| | | | (10) | | | | (0) | | | | (0) | | | | (10) | | | | | |
| | | | 7 | 3 | 0 | 0 | 3 | | | | | | | | 4 | 5 | 1 | 0 | 6 | |
| | | | 10 | 0 | 0 | 0 | 0 | | | | | | | | 9 | 1 | 0 | 0 | 1 | |
| | | | 6 | 4 | 0 | 0 | 4 | | | | | | | | 5 | 5 | 0 | 0 | 5 | |
| Hematopoietic system | | | | | | | | | | | | | | | | | | | | |
| Thymus | | | | | | | | | | | | | | | | | | | | |
| | | | (10) | | | | (0) | | | | (0) | | | | (10) | | | | | |
| | | | 1 | 8 | 1 | 0 | 9 | | | | | | | | 1 | 9 | 0 | 0 | 9 | |
| | | | NR (10) | | | | (0) | | | | (0) | | | | NR (10) | | | | | |
| | | | (1) | | | | (0) | | | | (0) | | | | (1) | | | | | |
| | | | 0 | 1 | 0 | 0 | 1 | | | | | | | | 0 | 1 | 0 | 0 | 1 | |
| | | | NR (10) | | | | (0) | | | | (0) | | | | NR (10) | | | | | |
| | | | (10) | | | | (0) | | | | (0) | | | | (10) | | | | | |
| | | | 9 | 1 | 0 | 0 | 1 | | | | | | | | 10 | 0 | 0 | 0 | 0 | |
| | | | 10 | 0 | 0 | 0 | 0 | | | | | | | | 10 | 0 | 0 | 0 | 0 | |
| | | | 10 | 0 | 0 | 0 | 0 | | | | | | | | 10 | 0 | 0 | 0 | 0 | |
| | | | (10) | | | | (0) | | | | (0) | | | | (10) | | | | | |
| | | | 10 | 0 | 0 | 0 | 0 | | | | | | | | 10 | 0 | 0 | 0 | 0 | |

Not significantly different from control.

Grade sign: -, none; +, mild; ++, moderate; +++, marked.

NR: no remarkable changes.

Figures in parentheses are number of animals with tissues examined histopathologically.

Two males in the 0.1 mg/kg group died.

Table 16 - continued Histopathological findings
Male, Female, 52w

| Organs and findings | Sex | | Male | | | | | | | | | | | | | | | | | |
|---|-------------------|---|---------|-----|-------|---|-----------|----|-----|-------|-----------|---|----|-----|-----------|---|---|----|-----|-------|
| | Group and dose | | Control | | | | 0.1 mg/kg | | | | 0.5 mg/kg | | | | 2.5 mg/kg | | | | | |
| | Number of animals | | 10 | | | | 8 | | | | 10 | | | | 10 | | | | | |
| | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total |
| Hematopoietic system | | | | | | | | | | | | | | | | | | | | |
| Bone marrow (femur) | | | | | | | | | | | | | | | | | | | | |
| Atrophy, focal | | | | | | | | | | | | | | | | | | | | |
| Hematopoiesis, increased | | | | | | | | | | | | | | | | | | | | |
| Cardiovascular system | | | | | | | | | | | | | | | | | | | | |
| Heart | | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, mononuclear cell | | | | | | | | | | | | | | | | | | | | |
| Fibrosis, myocardium | | | | | | | | | | | | | | | | | | | | |
| Aorta | | | | | | | | | | | | | | | | | | | | |
| Urinary system | | | | | | | | | | | | | | | | | | | | |
| Kidney | | | | | | | | | | | | | | | | | | | | |
| Hyperplasia, epithelial cell, tubule | | | | | | | | | | | | | | | | | | | | |
| Hyperplasia, transitional cell, pelvis | | | | | | | | | | | | | | | | | | | | |
| Tubule, basophilic | | | | | | | | | | | | | | | | | | | | |
| Cast, proteinaceous | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage, pelvis | | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, mononuclear cell, pelvis | | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, mononuclear cell, cortex | | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, pelvis, neutrophil | | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, cortex, neutrophil | | | | | | | | | | | | | | | | | | | | |
| Cellular exudation, pelvic cavity, neutrophil | | | | | | | | | | | | | | | | | | | | |
| Mineralization, papilla | | | | | | | | | | | | | | | | | | | | |
| Mineralization, pelvis | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, muscular layer, neutrophil | | | | | | | | | | | | | | | | | | | | |

Not significantly different from control.
Grade sign: -, none; +, mild; ++, moderate; +++, marked.
NR: no remarkable changes.
Figures in parentheses are number of animals with tissues examined histopathologically.
Two males in the 0.1 mg/kg group died.

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Table 16 - continued Histopathological findings
Male, Female, 52w

| Organs and findings | Sex Group and dose Number of animals | Male | | | | | | | | | | | | | | | | | | | |
|--|--|---------|---|----|-----|-------|-----------|---|----|-----|-------|-----------|---|----|-----|-------|-----------|---|----|-----|-------|
| | | Control | | | | | 0.1 mg/kg | | | | | 0.5 mg/kg | | | | | 2.5 mg/kg | | | | |
| | | 10 | | | | | 8 | | | | | 10 | | | | | 10 | | | | |
| | | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total |
| Genital system | | | | | | | | | | | | | | | | | | | | | |
| Testis | | | | | | | | | | | | | | | | | | | | | |
| (10) | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | |
| (10) | | | | | | | | | | | | | | | | | | | | | |
| Atrophy, seminiferous tubule | | | | | | | | | | | | | | | | | | | | | |
| Hyperplasia, leydig cell, focal | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | | | | | | | | | | | | | | | | | | | | | |
| (10) | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | |
| (10) | | | | | | | | | | | | | | | | | | | | | |
| Decrease, sperm, lumen | | | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, mononuclear cell | | | | | | | | | | | | | | | | | | | | | |
| Prostate | | | | | | | | | | | | | | | | | | | | | |
| (10) | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | |
| (10) | | | | | | | | | | | | | | | | | | | | | |
| Atrophy | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, mononuclear cell | | | | | | | | | | | | | | | | | | | | | |
| Seminal vesicle | | | | | | | | | | | | | | | | | | | | | |
| NR (10) | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | |
| Ovary | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | |
| Dilatation, ovarian bursa | | | | | | | | | | | | | | | | | | | | | |
| Cyst | | | | | | | | | | | | | | | | | | | | | |
| Uterus | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | |
| Metaplasia, epithelial cell, gland, squamous | | | | | | | | | | | | | | | | | | | | | |
| Polyp, endometrial stromal | | | | | | | | | | | | | | | | | | | | | |
| Vagina | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | | | | |
| Degeneration, epithelium, mucous | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | | | | | | | | | | | | | | | | | | | | | |
| (10) | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | |
| (0) | | | | | | | | | | | | | | | | | | | | | |
| (10) | | | | | | | | | | | | | | | | | | | | | |
| Hyperplasia, lobular | | | | | | | | | | | | | | | | | | | | | |
| Ectasia, alveolus/duct | | | | | | | | | | | | | | | | | | | | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | |
| Fibroadenoma | | | | | | | | | | | | | | | | | | | | | |
| Adenocarcinoma | | | | | | | | | | | | | | | | | | | | | |

Not significantly different from control.
Grade sign: -, none; +, mild(existent of tumor); ++, moderate; +++, marked.
NR: no remarkable changes.
NA: not applicable.
Figures in parentheses are number of animals with tissues examined histopathologically.
Two males in the 0.1 mg/kg group died.

Table 16 - continued
Histopathological findings
Male, Female, 52w

| Organs and findings | Sex Group and dose Number of animals | Male | | | | | | | | | | | | | | | | | |
|---|--|---------|---|----|-----|-----------|---|---|----|-----------|-------|---|---|-----------|-----|-------|---|---|----|
| | | Control | | | | 0.1 mg/kg | | | | 0.5 mg/kg | | | | 2.5 mg/kg | | | | | |
| | | 10 | | | | 8 | | | | 10 | | | | 10 | | | | | |
| | | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ |
| Endocrine system | | | | | | | | | | | | | | | | | | | |
| Pituitary | | | | | | | | | | | | | | | | | | | |
| Hyperplasia, anterior lobe | | | | | | | | | | | | | | | | | | | |
| Cyst, anterior lobe | | | | | | | | | | | | | | | | | | | |
| Thyroid | | | | | | | | | | | | | | | | | | | |
| Hyperplasia, C cell | | | | | | | | | | | | | | | | | | | |
| Deposit, material, interstitium, eosinophilic | | | | | | | | | | | | | | | | | | | |
| Remnant, ultimobranchial body | | | | | | | | | | | | | | | | | | | |
| Parathyroid | | | | | | | | | | | | | | | | | | | |
| Adrenal | | | | | | | | | | | | | | | | | | | |
| Hypertrophy, cortical cell, focal | | | | | | | | | | | | | | | | | | | |
| Hyperplasia, cortical cell, focal | | | | | | | | | | | | | | | | | | | |
| Angiectasis | | | | | | | | | | | | | | | | | | | |
| Nervous system | | | | | | | | | | | | | | | | | | | |
| Cerebrum | | | | | | | | | | | | | | | | | | | |
| Cerebellum | | | | | | | | | | | | | | | | | | | |
| Medulla oblongata | | | | | | | | | | | | | | | | | | | |
| Spinal cord | | | | | | | | | | | | | | | | | | | |
| Optic nerve | | | | | | | | | | | | | | | | | | | |
| Sciatic nerve | | | | | | | | | | | | | | | | | | | |
| Special sense organs | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, lymphocyte | | | | | | | | | | | | | | | | | | | |
| Musculoskeletal system | | | | | | | | | | | | | | | | | | | |
| M. biceps femoris | | | | | | | | | | | | | | | | | | | |

Not significantly different from control.

Grade sign: -, none; +, mild; ++, moderate; +++, marked.

NR: no remarkable changes.

NA: not applicable.

Figures in parentheses are number of animals with tissues examined histopathologically.

Two males in the 0.1 mg/kg group died.

Table 16 - continued
Histopathological findings
Male, Female, 52w

| Organs and findings | Sex Group and dose Number of animals | Male | | | | | | | | | | | | | | | | | | | |
|------------------------|--|---------|---|----|-----|-----------|---|---|----|-----------|-------|---|---|-----------|-----|-------|---|---|----|-----|-------|
| | | Control | | | | 0.1 mg/kg | | | | 0.5 mg/kg | | | | 2.5 mg/kg | | | | | | | |
| | | 10 | | | | 8 | | | | 10 | | | | 10 | | | | | | | |
| | | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total |
| Musculoskeletal system | | | | | | | | | | | | | | | | | | | | | |
| Sternum | | NR(10) | | | | (0) | | | | (0) | | | | NR(10) | | | | | | | |
| Femur | | NR(10) | | | | (0) | | | | (0) | | | | NR(10) | | | | | | | |
| Integumentary system | | | | | | | | | | | | | | | | | | | | | |
| Integument | | NR(10) | | | | (0) | | | | (0) | | | | NR(10) | | | | | | | |
| Others | | | | | | | | | | | | | | | | | | | | | |
| Extremity | | (5) | | | | (0) | | | | (0) | | | | (1) | | | | | | | |
| Ulcer, hindlimb | | 0 | 4 | 1 | 0 | 5 | | | | | | 0 | 0 | 1 | 0 | 1 | | | | | |

Not significantly different from control.

Grade sign: -, none; +, mild; ++, moderate; +++, marked.

NR: no remarkable changes.

Figures in parentheses are number of animals with tissues examined histopathologically.

Two males in the 0.1 mg/kg group died.

Table 16 - continued Histopathological findings
Male, Female, 52w

| Organs and findings | Sex | | Female | | | | | | | | | | | | | | | | | |
|--|-------------------|---------|---------|-----|-------|-----|-----------|----|-----|-------|-----------|---|----|--------|------------|---|---|----|-----|-------|
| | Group and dose | | Control | | | | 0.5 mg/kg | | | | 2.5 mg/kg | | | | 12.5 mg/kg | | | | | |
| | Number of animals | | 10 | | | | 10 | | | | 10 | | | | 9 | | | | | |
| | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total |
| Digestive system | | | | | | | | | | | | | | | | | | | | |
| Tongue | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | |
| Esophagus | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | |
| Stomach | | (10) | | | | (0) | | | | (0) | | | | (9) | | | | | | |
| Dilatation, glandular space, glandular stomach | | 10 | 0 | 0 | 0 | 0 | | | | | | | | | 9 | 0 | 0 | 0 | 0 | |
| Cellular infiltration, mucosa, glandular stomach, neutrophil | | 10 | 0 | 0 | 0 | 0 | | | | | | | | | 8 | 1 | 0 | 0 | 1 | |
| Duodenum | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | |
| Jejunum | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | |
| Ileum | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | |
| Cecum | | (10) | | | | (0) | | | | (0) | | | | (9) | | | | | | |
| Fibrosis, muscular layer | | 10 | 0 | 0 | 0 | 0 | | | | | | | | | 8 | 1 | 0 | 0 | 1 | |
| Colon | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | |
| Rectum | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | |
| Submaxillary gland | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | |
| Sublingual gland | | NR (10) | | | | (0) | | | | (0) | | | | NR (9) | | | | | | |
| Parotid gland | | (10) | | | | (0) | | | | (0) | | | | (9) | | | | | | |
| Cellular infiltration, lymphocyte | | 10 | 0 | 0 | 0 | 0 | | | | | | | | | 8 | 1 | 0 | 0 | 1 | |
| Liver | | (10) | | | | (0) | | | | (10) | | | | (9) | | | | | | |
| Degeneration, hepatocyte, fatty, periportal | | 8 | 2 | 0 | 0 | 2 | | | | | 10 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 0 |
| Degeneration, cystic | | 10 | 0 | 0 | 0 | 0 | | | | | 10 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 0 |
| Necrosis, hepatocyte, focal | | 8 | 2 | 0 | 0 | 2 | | | | | 10 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 0 |
| Hypertrophy, hepatocyte ¹⁾ , centrilobular | | 10 | 0 | 0 | 0 | 0 | | | | | 10 | 0 | 0 | 0 | 0 | 5 | 4 | 0 | 0 | 4* |
| Hematopoiesis, extramedullary | | 8 | 2 | 0 | 0 | 2 | | | | | 10 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 0 |
| Focus, altered cell, basophilic | | 6 | 4 | 0 | 0 | 4 | | | | | 8 | 2 | 0 | 0 | 2 | 7 | 2 | 0 | 0 | 2 |
| Focus, altered cell, clear | | 10 | 0 | 0 | 0 | 0 | | | | | 10 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 0 |
| Deposit, lipofuscin ²⁾ , hepatocyte | | 10 | 0 | 0 | 0 | 0 | | | | | 10 | 0 | 0 | 0 | 0 | 7 | 2 | 0 | 0 | 2 |
| Angiectasis | | 10 | 0 | 0 | 0 | 0 | | | | | 10 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 0 |
| Cellular infiltration, mononuclear cell | | 10 | 0 | 0 | 0 | 0 | | | | | 10 | 0 | 0 | 0 | 0 | 8 | 1 | 0 | 0 | 1 |
| Adenoma, hepatocellular | | 10 | 0 | 0 | 0 | 0 | | | | | 10 | 0 | 0 | 0 | 0 | 8 | 1 | 0 | 0 | 1 |

*: P<0.05 (significantly different from control).
 Grade sign: -, none; +, mild(existent of tumor); ++, moderate; +++, marked.
 NR: no remarkable changes.
 1) with eosinophilic granular cytoplasm.
 2) identified by Schmorl method, Berlin blue staining and Hall method.
 Figures in parentheses are number of animals with tissues examined histopathologically.
 One female in the 12.5 mg/kg group died.

Table 16 - continued Histopathological findings
Male, Female, 52w

| Organs and findings | Sex | Group and dose | Female | | | | | | | | | | | | | | | | | | | |
|-----------------------------|-----|----------------|---|---|----|-----|-------|-----------|---|----|-----|-------|-----------|---|----|-----|-------|------------|---|----|-----|-------|
| | | | Control | | | | | 0.5 mg/kg | | | | | 2.5 mg/kg | | | | | 12.5 mg/kg | | | | |
| | | | 10 | | | | | 10 | | | | | 10 | | | | | 9 | | | | |
| | | | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total |
| Digestive system | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | | | | | | | | | | | | | | | | | | | | | | |
| | | | (10) | | | | | (0) | | | | | (0) | | | | | (9) | | | | |
| | | | 9 | 1 | 0 | 0 | 1 | | | | | | | | | | | | | | | |
| | | | Atrophy, acinus, focal | | | | | | | | | | | | | | | | | | | |
| | | | Hyperplasia, acinar cell, focal | | | | | | | | | | | | | | | | | | | |
| | | | Cellular infiltration, lymphocyte | | | | | | | | | | | | | | | | | | | |
| | | | Fibrosis, islet | | | | | | | | | | | | | | | | | | | |
| Respiratory system | | | | | | | | | | | | | | | | | | | | | | |
| Trachea | | | | | | | | | | | | | | | | | | | | | | |
| | | | (10) | | | | | (0) | | | | | (0) | | | | | (9) | | | | |
| | | | Cellular infiltration, lamina propria, neutrophil | | | | | | | | | | | | | | | | | | | |
| Lung | | | | | | | | | | | | | | | | | | | | | | |
| | | | (10) | | | | | (0) | | | | | (0) | | | | | (9) | | | | |
| | | | Accumulation, foam cell, alveolus | | | | | | | | | | | | | | | | | | | |
| | | | Pneumonia, aspiration | | | | | | | | | | | | | | | | | | | |
| | | | Mineralization, artery | | | | | | | | | | | | | | | | | | | |
| Hematopoietic system | | | | | | | | | | | | | | | | | | | | | | |
| Thymus | | | | | | | | | | | | | | | | | | | | | | |
| | | | (10) | | | | | (0) | | | | | (0) | | | | | (9) | | | | |
| | | | Atrophy | | | | | | | | | | | | | | | | | | | |
| | | | Submaxillary lymph node | | | | | | | | | | | | | | | | | | | |
| | | | Popliteal lymph node | | | | | | | | | | | | | | | | | | | |
| | | | Proliferation, plasma cell | | | | | | | | | | | | | | | | | | | |
| | | | Mesenteric lymph node | | | | | | | | | | | | | | | | | | | |
| Spleen | | | | | | | | | | | | | | | | | | | | | | |
| | | | NR (10) | | | | | (0) | | | | | (0) | | | | | NR (9) | | | | |
| | | | Thickening, capsule | | | | | | | | | | | | | | | | | | | |
| | | | Hematopoiesis, extramedullary | | | | | | | | | | | | | | | | | | | |
| | | | Deposit, pigment, red pulp, brown | | | | | | | | | | | | | | | | | | | |
| Bone marrow (sternum) | | | | | | | | | | | | | | | | | | | | | | |
| | | | (10) | | | | | (0) | | | | | (0) | | | | | (9) | | | | |
| | | | Atrophy, focal | | | | | | | | | | | | | | | | | | | |

Not significantly different from control.

Grade sign: -, none; +, mild; ++, moderate; +++, marked.

NR: no remarkable changes.

Figures in parentheses are number of animals with tissues examined histopathologically.

One female in the 12.5 mg/kg group died.

Table 16 - continued

Histopathological findings
Male, Female, 52w

| Organs and findings | Sex | | Female | | | | | | | | | | | | | | | | | |
|---|-------------------|---|---------|-----|-------|---|-----------|----|-----|-------|-----------|---|----|-----|------------|---|---|----|-----|-------|
| | Group and dose | | Control | | | | 0.5 mg/kg | | | | 2.5 mg/kg | | | | 12.5 mg/kg | | | | | |
| | Number of animals | | 10 | | | | 10 | | | | 10 | | | | 9 | | | | | |
| | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total |
| Hematopoietic system | | | | | | | | | | | | | | | | | | | | |
| Bone marrow (femur) | | | | | | | | | | | | | | | | | | | | |
| Atrophy, focal | | | | | | | | | | | | | | | | | | | | |
| Hematopoiesis, increased | | | | | | | | | | | | | | | | | | | | |
| Cardiovascular system | | | | | | | | | | | | | | | | | | | | |
| Heart | | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, mononuclear cell | | | | | | | | | | | | | | | | | | | | |
| Fibrosis, myocardium | | | | | | | | | | | | | | | | | | | | |
| Aorta | | | | | | | | | | | | | | | | | | | | |
| Urinary system | | | | | | | | | | | | | | | | | | | | |
| Kidney | | | | | | | | | | | | | | | | | | | | |
| Hyperplasia, epithelial cell, tubule | | | | | | | | | | | | | | | | | | | | |
| Hyperplasia, transitional cell, pelvis | | | | | | | | | | | | | | | | | | | | |
| Tubule, basophilic | | | | | | | | | | | | | | | | | | | | |
| Cast, proteinaceous | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage, pelvis | | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, mononuclear cell, pelvis | | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, mononuclear cell, cortex | | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, pelvis, neutrophil | | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, cortex, neutrophil | | | | | | | | | | | | | | | | | | | | |
| Cellular exudation, pelvic cavity, neutrophil | | | | | | | | | | | | | | | | | | | | |
| Mineralization, papilla | | | | | | | | | | | | | | | | | | | | |
| Mineralization, pelvis | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | | | | | | | | | | | | | | | | | | | | |
| Cellular infiltration, muscular layer, neutrophil | | | | | | | | | | | | | | | | | | | | |

Not significantly different from control.

Grade sign: -, none; +, mild; ++, moderate; +++, marked.

NR: no remarkable changes.

Figures in parentheses are number of animals with tissues examined histopathologically.

One female in the 12.5 mg/kg group died.

Table 16 - continued
Histopathological findings
Male, Female, 52w

| Organs and findings | Sex | Group and dose | Number of animals | Female | | | | | | | | | | | | | | | | | | | | |
|------------------------|-----|---|-------------------|---------|---|---------|-----|-------|-----------|---|----|-----|-------|-----------|-----|----|-----|-------|------------|-----|--------|-----|-------|---|
| | | | | Control | | | | | 0.5 mg/kg | | | | | 2.5 mg/kg | | | | | 12.5 mg/kg | | | | | |
| | | | | 10 | | | | | 10 | | | | | 10 | | | | | 9 | | | | | |
| | | | | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | |
| Endocrine system | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | (10) | | | | | (0) | | | | | | (0) | | | | | (9) | | | | |
| | | Hyperplasia, anterior lobe. | 7 | 3 | 0 | 0 | 3 | | | | | | | | | | | | | 6 | 3 | 0 | 0 | 3 |
| | | Cyst, anterior lobe | 10 | 0 | 0 | 0 | 0 | | | | | | | | | | | | | 9 | 0 | 0 | 0 | 0 |
| Thyroid | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | (10) | | | | | (0) | | | | | | (0) | | | | | | (9) | | | |
| | | Hyperplasia, C cell | 10 | 0 | 0 | 0 | 0 | | | | | | | | | | | | | 8 | 1 | 0 | 0 | 1 |
| | | Deposit, material, interstitium, eosinophilic | 10 | 0 | 0 | 0 | 0 | | | | | | | | | | | | | 9 | 0 | 0 | 0 | 0 |
| | | Remnant, ultimobranchial body | 8 | 2 | 0 | 0 | 2 | | | | | | | | | | | | | 8 | 1 | 0 | 0 | 1 |
| Parathyroid | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | NR (10) | | | | | (0) | | | | | | (0) | | | | | | NR (9) | | | |
| Adrenal | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | (10) | | | | | (0) | | | | | | (0) | | | | | | (9) | | | |
| | | Hypertrophy, cortical cell, focal | 8 | 2 | 0 | 0 | 2 | | | | | | | | | | | | | 7 | 2 | 0 | 0 | 2 |
| | | Hyperplasia, cortical cell, focal | 6 | 4 | 0 | 0 | 4 | | | | | | | | | | | | | 8 | 1 | 0 | 0 | 1 |
| | | Angiectasis | 6 | 4 | 0 | 0 | 4 | | | | | | | | | | | | | 8 | 1 | 0 | 0 | 1 |
| Nervous system | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Cerebrum | | | | NR (10) | | | (0) | | | | | | (0) | | | | | | NR (9) | | | |
| | | Cerebellum | | | | NR (10) | | | (0) | | | | | | (0) | | | | | | NR (9) | | | |
| | | Medulla oblongata | | | | NR (10) | | | (0) | | | | | | (0) | | | | | | NR (9) | | | |
| | | Spinal cord | | | | NR (10) | | | (0) | | | | | | (0) | | | | | | NR (9) | | | |
| | | Optic nerve | | | | NR (10) | | | (0) | | | | | | (0) | | | | | | NR (9) | | | |
| | | Sciatic nerve | | | | NR (10) | | | (0) | | | | | | (0) | | | | | | NR (9) | | | |
| Special sense organs | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Eye | | | | NR (10) | | | (0) | | | | | | (0) | | | | | | NR (9) | | | |
| | | Harderian gland | | | | (10) | | | (0) | | | | | | (0) | | | | | | (9) | | | |
| | | Cellular infiltration, lymphocyte | 10 | 0 | 0 | 0 | 0 | | | | | | | | | | | | | 8 | 1 | 0 | 0 | 1 |
| Musculoskeletal system | | | | | | | | | | | | | | | | | | | | | | | | |
| | | M. biceps femoris | | | | NR (10) | | | (0) | | | | | | (0) | | | | | | NR (9) | | | |

Not significantly different from control.

Grade sign: -, none; +, mild; ++, moderate; +++, marked.

NR: no remarkable changes.

Figures in parentheses are number of animals with tissues examined histopathologically.

One female in the 12.5 mg/kg group died.

Table 16 - continued

Histopathological findings
Male, Female, 52w

| Organs and findings | Sex Group and dose Number of animals | Female | | | | | | | | | | | | | | | | | | | |
|------------------------|--|---------|---|----|-----|-----------|---|---|----|-----------|-------|---|---|------------|-----|-------|---|---|----|-----|--------|
| | | Control | | | | 0.5 mg/kg | | | | 2.5 mg/kg | | | | 12.5 mg/kg | | | | | | | |
| | | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total | - | + | ++ | +++ | Total |
| Musculoskeletal system | | | | | | | | | | | | | | | | | | | | | |
| Sternum | | | | | | NR (10) | | | | | (0) | | | | | (0) | | | | | NR (9) |
| Femur | | | | | | NR (10) | | | | | (0) | | | | | (0) | | | | | NR (9) |
| Integumentary system | | | | | | | | | | | | | | | | | | | | | |
| Integument | | | | | | NR (10) | | | | | (0) | | | | | (0) | | | | | NR (9) |
| Others | | | | | | | | | | | | | | | | | | | | | |
| Exiremity | | | | | | (1) | | | | | (0) | | | | | (0) | | | | | (2) |
| Ulcer, hindlimb | | 0 | 1 | 0 | 0 | 1 | | | | | | | | | | | 0 | 2 | 0 | 0 | 2 |

Not significantly different from control.

Grade sign: -, none; +, mild; ++, moderate; +++, marked.

NR: no remarkable changes.

Figures in parentheses are number of animals with tissues examined histopathologically.

One female in the 12.5 mg/kg group died.